32– Chronic Hepatitis

Speaker: David Thomas, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Chronic Hepatitis

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7/10/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

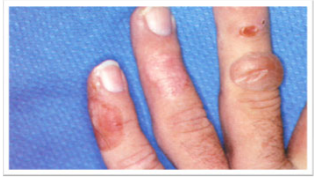
- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck and Excision Bio

Chronic Hepatitis and Liver Disease

- HCV
- HBV (and delta)
- Other forms
- HIV coinfection

Case: Hepatitis C and a rash

A 44 year old, anti-HCV and HCV RNA positive man feels bad after a recent alcohol binge. He has a chronic rash on arms that is worse and elevated ALT and AST.



OConnor Mayo Clin Proc 1998

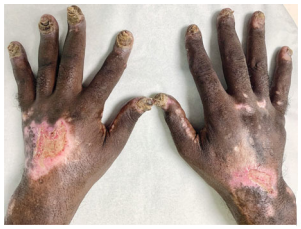
Question: HCV with a rash

The most likely dx is:

A. Cirrhosis due to HCV and alcohol
B. Necrolytic acral erythema
C. Porphyria cutanea tarda
D. Essential mixed cryoglobulinemia
E. Yersinia infection

Porphyria Cutanea Tarda Associated with Hepatitis C

Tejesh S. Patel, M.D., and Evgeniya Teterina Mohammed, M.D.



June 10, 2021
N Engl J Med 2021; 384:e86

32– Chronic Hepatitis

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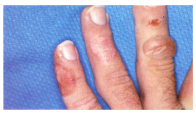
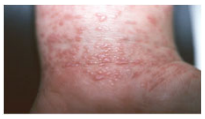
Compare

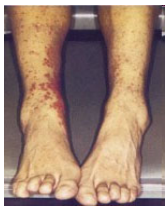
Porphyria cutanea tarda



Lichen planus



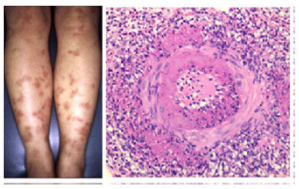
Cryoglobulin vasculitis



blogspot.com; OConnor Mayo Clin Proc 1998

Case: HBV and rash

46 year old woman HBsAg pos, anti-HCV neg



Chen Rheum 2014

Question: HBV with a rash

The most likely dx is:

A. **Necrolytic acral erythema**
B. **Porphyria cutanea tarda**
C. **Essential mixed cryoglobulinemia**
D. **Polyarteritis nodosa**
E. **Secondary syphilis vasculitis**

Question: Who needs an HCV antibody test?

A. **33 year old woman with normal ALT and negative test during pregnancy at 28**
B. **55 year old man with new exposure after HCV treatment**
C. **24 year old pregnant woman with no risk factors**
D. **Former PWID who was HCV negative 1 yr ago**
E. **HIV positive MSM with negative HCV antibody test 5 years ago and no risk factors**

IDSA/AASLD guidelines

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.	IIa, C

USPSTF 2020

RECOMMENDATION The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

JAMA. doi:10.1001/jama.2020.1123
Published online March 2, 2020.

PREVIEW QUESTION

Case: 54 y/o with HCV antibodies and RNA

54 year old man was anti-HCV pos after elevated ALT noted by primary. Brief IDU when 20-21; moderate ETOH; otherwise well.

HCV RNA 4 million IU/L; Genotype 1a; ALT 42 IU/ml; AST 65 IU/ml; TB 1.6 mg/dl; Alb 3.9 mg/dl; Hb – 13.4 mg/dl; creatinine 1.2 mg/dl; HBsAg pos; anti-HBc pos. HIV neg

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PREVIEW QUESTION

Question: 54 y/o with HCV antibodies and RNA

Which of the following is the next appropriate step:

A. Treat with oral regimen for 8-12 weeks
B. Check HCV 1a resistance test
C. Elastography
D. Confirm HCV antibody test

HCV NS5 RAS testing is uncommonly recommended

Treatment naive	*Treatment experienced*
• Genotype 1a and elbasvir/grazoprevir	• 1a and ledipasvir/sofosbuvir 'considered'
• Genotype 3 AND cirrhosis for sofosbuvir/velpatasvir	• Genotype 3 and sofosbuvir/velpatasvir

NB: no PI resistance testing
Clinically sig is >100-fold in vitro

Wyles, HCVguidelines.org

Staging is needed for chronic HCV

Accepted staging methods	Not for routine staging
1. Liver biopsy	1. Viral load
2. Blood markers	2. HCV genotype
3. Elastography	3. Ultrasound
4. Combinations of 1-3	4. CT scan or MRI

Hcvguidelines.org

$$\text{FIB 4} = \frac{\text{Age (yrs) x AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x ALT (U/L)}^{1/2}}$$

847 liver biopsies with chronic HCV

	Liver Biopsy (METAVIR)		
FIB4 Index	F0-F1-F2	F3-F4	Total
<1.45	94.7% (n = 521)	5.3% (n = 29)	550
1.45-3.25	73.0% (n = 168)	27.0% (n = 62)	230
>3.25	17.9% (n = 12)	82.1% (n = 55)	67
Total	82.8% (n = 701)	17.2% (n = 146)	847

Sterling Hepatology 2006; Vallet-Pichard Hepatology 2007

Of imperfect tests elastography is most sensitive for detection of cirrhosis

Test	% Sens	% Spec	AUROC
Fibrotest[1] >.56	85	74	.86
Fibrotest > .73	56	81	-
FIB4[2], >1.45	87	61	.87
APRI[3], >1.0	51	91	0.73
Elastography 12.5 kPa	89	91	0.95

Singh Gastro 2017; Chou Ann Intern Med 2013; Castera Gastro 2012

Case con't: 54 year old with HCV

Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis. Ultrasound and UGI are ok and you recommend treatment. He wants to know why. Which can you NOT say is true of successful treatment?

A. reduces risk of reinfection
B. reduces risk of death
C. reduces risk of HCC
D. reduces risk of liver failure

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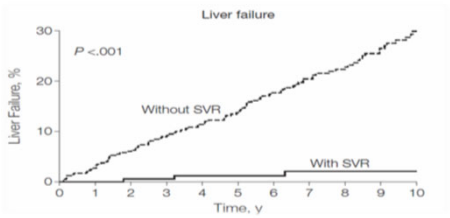
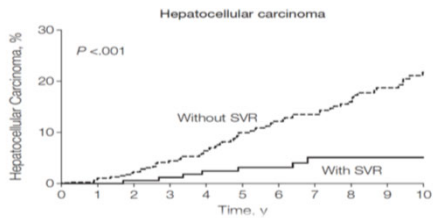
SVR reduces clinical outcomes



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR reduces clinical outcomes



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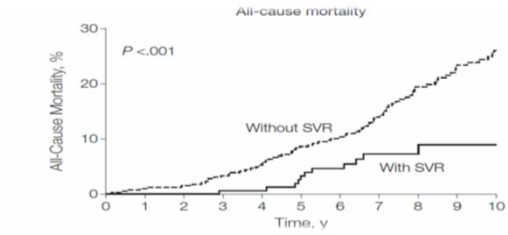
SVR reduces clinical outcomes



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AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA Infectious Diseases Society of America

Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations

Recommended 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 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
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

54 y/o with HCV antibodies, RNA, and cirrhosis

Treatment is given with glecaprevir and pibrentasvir

Treatment week 8: HCV RNA undet; ALT 1279 IU/L; AST 987 IU/L; TB 3.2 mg/dl.

Which test is likely to be most helpful?

A. Glecaprevir level
B. HCV resistance test
C. HCV IRIS T cell marker
D. HBV DNA
E. Liver biopsy with EM

U.S. Food and Drug Administration Protecting and Promoting Your Health — **Drug Safety Communications**

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

All are tested for HBV

- HBsAg pos: treat per HBV guidelines
- Anti-HBc pos: monitor

Bersoff-Macha Ann Intern Med 2017; Thio and Balagopal CID 2015

32– Chronic Hepatitis

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Which is NOT a pangenotypic regimen?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

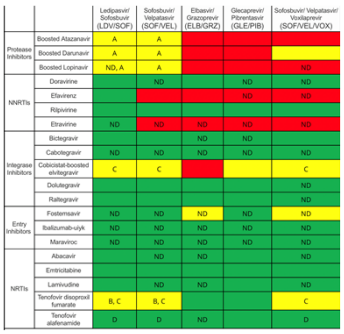
Which regimen is approved for ESRD?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. All of the above

Which regimen is worst with darunavir?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

HCV-HIV ART drug interactions



		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease Inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	Bictegravir			ND	ND	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

www.hcvguidelines.com

Slide 28 of 44

HCV treatment summary 2022

- Test, stage, and treat
- Two pangenotypic regimens: SOF/VEL and GP
- Watch for HBV relapse at week 8
- No change for HIV (avoid drug interactions), renal insufficiency, acute infection
- Compensated cirrhosis same for G/P and Sof-based except GT3 with resistance

Case of chronic hepatitis B

31 yr old Asian woman is referred to see you because she had a positive HBsAg test. She is otherwise feeling fine.

HBsAg pos, HBeAg neg, anti-HBe pos, ALT 78 IU/ml, AST 86 IU/ml, TB 0.8, albumin 4.2 g/dl, INR 1.

32– Chronic Hepatitis

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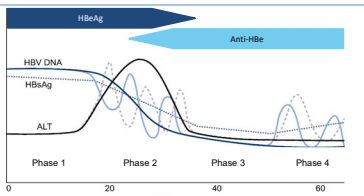
Which of the following tests is NOT recommended?

A. HIV test
B. HBV resistance
C. HBV genotype
D. Hepatitis Delta testing
E. Quantitative HBV DNA level

The essential evaluation of persons with CHB

- HBeAg, HIV, HBV DNA, delta, genotype
- Stage (liver enzymes and/or elastography or biopsy)
- Renal status
- US to r/o HCC
  - Asian: male 40; female 50
  - African: 25-30

Use testing to define disease phase[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Use testing to define disease phase

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Use disease phase to determine whom to treat

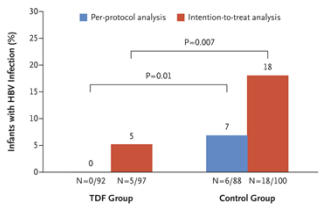
Chronic HBV infection	HBeAg positive		HBeAg negative	
	Phase 1	Phase 2	Phase 3	Phase 4
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated†

Treat with both high DNA and ALT

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Test pregnant women for HBsAg and, if pos, for HBV DNA* and treat if > 200,000 IU/ml

Rec for all pregnant women to have quantitative HBV DNA TEST



*test in 3rd trimester

Terrault Hepatology 2015; Pan NEJM 2016

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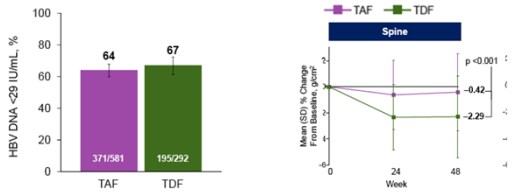
Four preferred treatments for chronic hepatitis B

HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7 11 (at 3 years posttreatment)	4-5	8	1
HBeAg Negative	**Peg-IFN**	**Entecavir**	**Tenofovir Disoproxil Fumarate†**	**Tenofovir Alafenamide‡**
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)‖	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 IU/mL)	90 (<29 IU/mL)
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4 6 (at 3 years posttreatment)	0-1	0	<1

TAF 25 mg with or without FTC

AASLD guidelines, Terrault Hepatology 2018

TAF is as effective and safer than tenofovir DF for chronic hepatitis B



Chan Lancet Gastro 2016

Treatment of HBV changes with renal insufficiency

- **GFR 30-60 mL/min/1.73 m²** : TAF 25 mg preferred
- **GFR <30-10:** TAF 25mg OR entecavir 0.5 mg q 3d
- **GFR <10 no dialysis:** entecavir 0.5 mg
- **Dialysis:** TDF 300mg/wk PD or entecavir 0.5mg/wk or TAF 25mg PD

It is hard to stop HBV treatment

- **If HBeAg conversion noted and no cirrhosis *consider* stopping after 6 months**
- **HBeAg neg when treatment started and all with cirrhosis stay on indefinitely**

HIV/HBV coinfected need treatment for both

- **<u>All</u> are treated and tested for both**
- **HBV-active ART**
- **Entecavir less effective if LAM exposure**
- **Watch switch from TAF- or TDF-containing regimen**

What if HBV levels stay detectable?

- **Continue monotherapy, ideally with TAF or TDF**
- **Rising levels (breakthrough)**
  - **Add second drug or switch esp if initial Rx with ETV**

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2022 PREVIEW QUESTION

Hepatitis serology in the oncology suite

You are called about 62 year old Vietnamese scientist who is in oncology suite where he is about to get R-CHOP for Non Hodgkins lymphoma.

Baseline labs: normal AST, ALT, and TBili. Total HAV detectable; anti-HBc pos; HBsAg neg; anti-HCV neg.

2022 PREVIEW QUESTION

What do you recommend?

A. Hold rituximab
B. Hold prednisone
C. Entecavir 0.5 mg
D. HCV PCR
E. HBV DNA

Rituximab, high-dose prednisone, and BM transplant high risk for HBV reactivation

- If HBsAg pos, prophylaxis *always* recommended
- If anti-HBc pos but HBsAg neg, prophylaxis still recommended with high risk exposures
- Use TAF or ETV

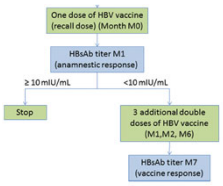
AASLD Terrault Hepatology 2018

Isolated anti-core antibodies usually reflect occult hepatitis B in high risk groups

- Primary responses to vaccination
- 29 anti-HBc and 40 negative for anti-HBc
  - anamnestic response in anti-HBc pos (24%) vs anti-HBc neg (10%)
  - 50% anti-HBc pos also tested positive for anti-HBe
  - Anti-HBs seroconversion in ~60% both groups

Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV vaccination recommended in persons with isolated anti-HBc



Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV Prevention is with vaccine and sometimes HBIG

Pre-exposure:

- vaccinate ALL < 60 yrs and get post vaccination titers (<2 months) if exposure likely
- Engerix; Recombivax; Heplisav (2 dose); PreHevbrio; Twinrix

Post Exposure:

- vaccinate if not already done or not known to respond
- add HBIG when infection likely
- infants of HBsAg pos mothers get immediate vaccination and HBIG

MMWR April 1, 2022 71 (13) 477-483; MMWR / January 12, 2018 / Vol. 67 / No. 1

32– Chronic Hepatitis

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Chronic Hepatitis for the Boards Summary

- HCV-associated conditions: PCT or cryoglobulinemia
- HBV-associated: PAN
- HCV: staging or treatment outcome
- HBV: relapse post rituximab
- Guess b and good luck

Thanks and good luck on the test!

Questions:

Dave Thomas

–dthomas@jhmi.edu

BONUS CASE

A final case of chronic hepatitis in transplant recipient

51 y/o HTN, and ankylosing spondylitis s/p renal transplant presents with elevated liver enzymes. Pred 20/d; MMF 1g bid; etanercept 25mg twice/wk; tacro 4mg bid. Hunts wild boar in Texas

HBsAg neg, anti-HBs pos, anti-HBc neg; anti-HCV neg; HCV RNA neg; CMV IgG neg; EBV neg; VZV neg. ALT 132 IU/ml, AST 65 IU/ml; INR 1. ALT and AST remained elevated; HBV, HCV, HAV, CMV, EBV serologies remain neg.

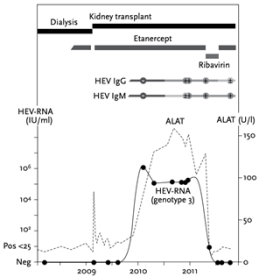
Barrague Medicine 2017

Which test is most likely abnormal

1. HEV PCR
2. HCV IgM
3. Tacrolimus level
4. Adenovirus PCR
5. Delta RNA PCR

Chronic HEV in transplant recipient

- Europe (boar)
- Can cause cirrhosis
- Tacrolimus associated
- Ribavirin may be effective



Barrague Medicine 2017