The ABC of Hepatitis

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Case # 1

- 24 year male, returned from a trip to India, has a 1 week H/O malaise, nausea, mild abdominal pain. CBC-normal, ALT 1500, AST-900, Alk PO4-254, Bil-5.6
- Diagnosis ?

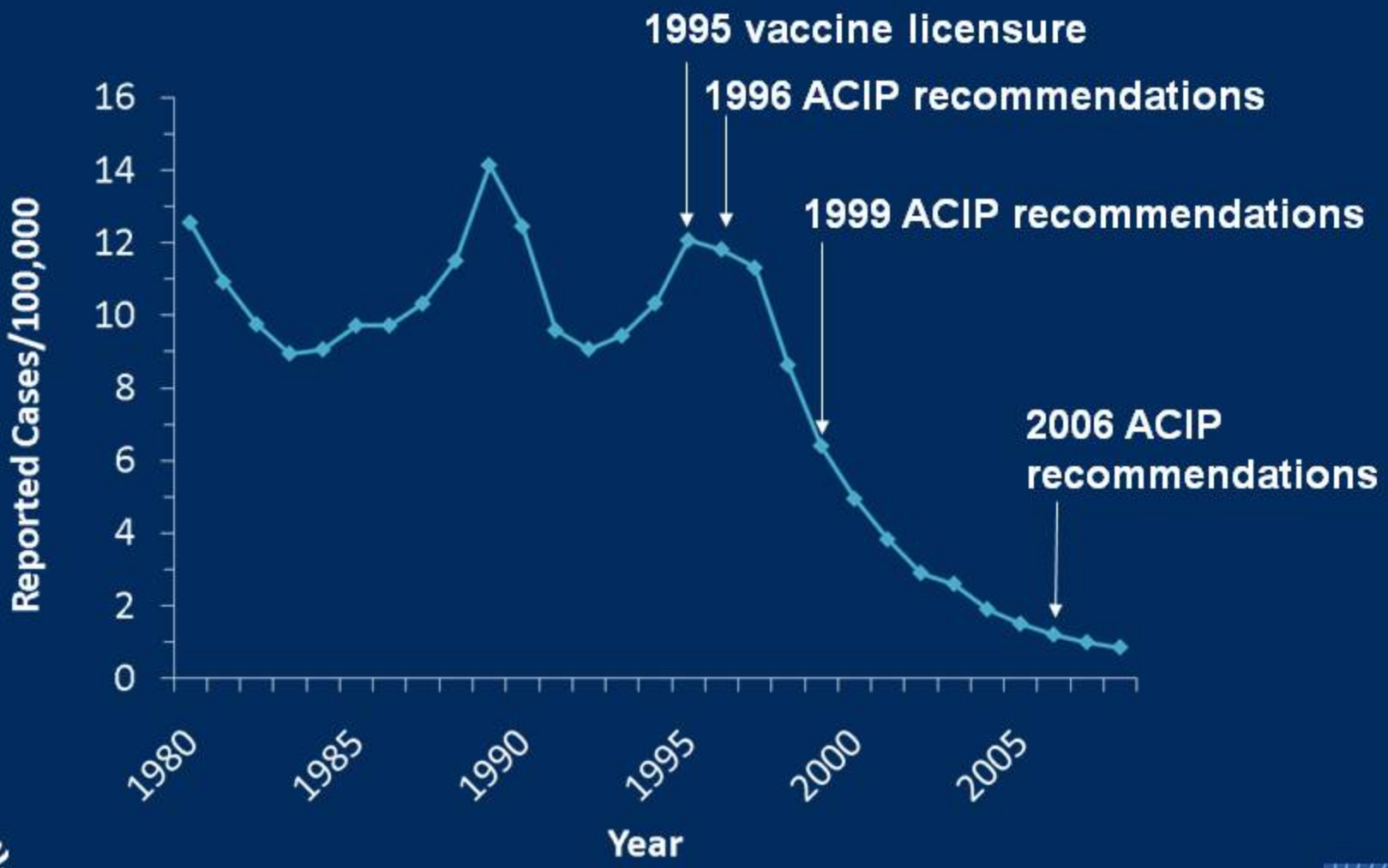
Differential Diagnosis of Acute Hepatitis

Viral infections	hepatitis A, B, C, D, and E, CMV, EBV, HSV, VZV, yellow fever
Bacterial infections	typhoid fever, Q fever, RMSF, leptospirosis, secondary syphillis, sepsis
Parasitic infections	toxocariasis, liver flukes
Drugs	ASA, acetaminophen, INH, rifampin, oral contraceptives, anti-seizure carbenicillin, sulfonamides
Toxins	Alcohol, carbon tetrachloride
Autoimmune diseases	Autoimmune hepatitis, SLE

Basic Features of Hepatitis Viruses

Virus	Transmission	Incubation Period (weeks)	Chronic Infection
A	fecal-oral	4 (2-6)	No
B	parenteral	8-12 (6-24)	Yes
C	parenteral	6-9 (2-24)	Yes
D	parenteral	? (2-10)	Yes
E	fecal-oral	4-5 (2-9)	No

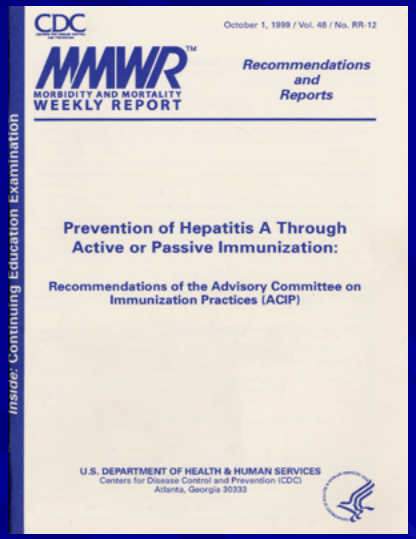
Incidence of Acute, Symptomatic Hepatitis A — United States, 1980–2008



Source: National Notifiable Diseases Surveillance System (NNDSS)

ACIP Recommendations – Hepatitis A Vaccine
Pre-exposure Vaccination

- Persons at increased risk for infection
  - travelers to intermediate and high HAV-endemic countries
  - MSM (Men who have sex with men)
  - Illegal drug users
  - Persons who have clotting factor disorders
  - Persons with chronic liver disease
  - Communities with historically high rates of HAV
- Routine childhood vaccination
- Indicated for “anyone who wants protection”



Hepatitis A Vaccine Immunogenicity, Side Effects

- **Immunogenicity in children, adolescents, adults:**
  - ✓**94-100% positive 1 month after dose 1**
  - ✓**99-100% positive after dose 2**
- **Most common side effects:**
  - ✓**Sore injection site (50%), headache (15%), malaise**
  - ✓**No severe reactions known**
  - ✓**Safety in pregnancy unknown (risk likely is low)**

Currently licensed for adults

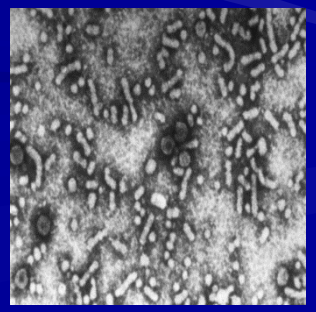
Hepatitis B

- 2 billion people worldwide have been infected
- Leading cause of cirrhosis and HCC worldwide

- Incubation period: Mean: 60-90 days

- Chronic infection: <5 yrs, 30%-90%
  ≥ 5 yrs, 2%-10%

- Premature mortality from chronic liver disease: 15%-25%



Interpretation of Serologic Results

HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
Negative	Negative	--	Negative	Susceptible; offer vaccination
Negative	Positive	--	Positive	Immune due to natural infection
Negative	Negative	--	Positive	Immune due to hepatitis B vaccination
Positive	Positive	Negative	Negative	Chronic HBV infection
Positive	Positive	Positive	Negative	Acute HBV infection
Negative	Positive	--	Negative	Unclear; could be any one of the following: 1. Resolved infection (most common) 2. False-positive anti-HBc; susceptible 3. “Low-level” chronic infection 4. Resolving acute infection

CDC. Hepatitis B FAQs for Health Professionals.

Interpret the serology

Test	Result
HBsAg	Negative
Anti-HBc	Negative
Anti-HBc-IgM	Negative
Anti-HBs	Positive
Anti-HBs Ratio	23.1

1. Chronic Hepatitis B?
2. Acute Hepatitis B?
3. Immunized?
4. False positive test?

Interpret the serology

Test	Result
HBsAg	Positive
Anti-HBc	Positive
Anti-HBc-IgM	Negative
Anti-HBs	Negative

1. Chronic Hepatitis B?
2. Acute Hepatitis B?
3. Immunized?
4. False positive test?

Therapies for HBV Infection

- Interferon
- Nucleoside analogues
  - Lamivudine- 100 mg qd
  - Entecavir -0.5 mg qd; 1 mg if lamivudine experienced
  - Telbivudine- 600 mg PO daily
  - Tenofovir- 300 mg PO daily
- Nucleotide analogues
  - Adefovir- 10 mg qd

General comments on HepB therapy

- Counsel avoidance of alcohol
- Vaccinate against hepatitis A (if not immune)
- On Treatment:
  - HepB eAg seroconversion is seen in 20-25%
  - HepB sAg seroconversion to HBsAb in <3% (More in Western populations- upto 20%)
  - Complete virological supression (HBV DNA) is seen in upto 90% with oral nucleotid(s)e therapy
  - Improves long term survival

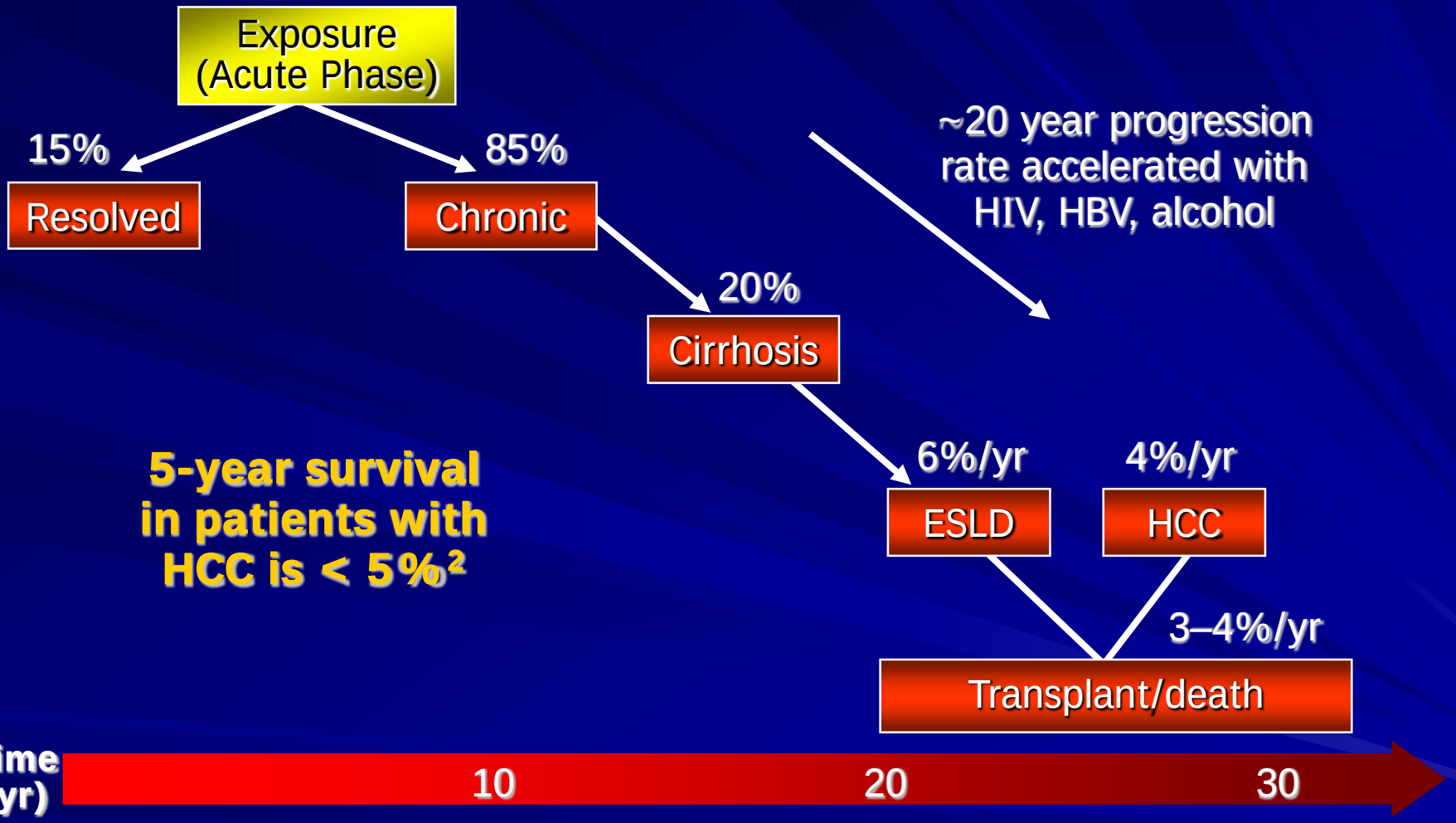
Hepatitis B Vaccine

- Licensed in 1982; currently recombinant (in US)
- 3 dose series, typical schedule 0, 1-2, 4-6 months - no maximum time between doses (no need to repeat missed doses or restart)
- 2 dose series (adult dose) licensed by FDA for 11-15 year olds (Merck)
- Protection ~30-50% dose 1; 75% - 2; 96% - 3; lower in older, immunosuppressive illnesses (e.g., HIV, chronic liver diseases, diabetes), obese, smokers

Hepatitis C

- **May 3, 2016:**
- Hepatitis C Kills More Americans than Any Other Infectious Disease
- Annual Hepatitis C-related mortality in 2013 surpassed the total combined number of deaths from 60 other infectious diseases reported to CDC, including HIV, pneumococcal disease, and tuberculosis.

Natural History of HCV Infection



5-year survival in patients with HCC is < 5%[2]

HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

Case

- 56 year male, diabetes mellitus, hypertension, dyslipidemia, non smoker, occasional alcohol, no history of drugs. In the office for a routine follow up visit. He has never been tested for Hepatitis C.

Q1. Would you screen him for Hepatitis C?

Q2. If so, what is the testing algorithm?

Question

- What percentage of the US population has Chronic HCV?
- 1.15%
- 2. 25%
- 3. 1%
- 4. 10%

Screening Recommendations

- >1% of the US population (3-4 million) has Chronic Hepatitis C
- Peak prevalence : (4.3%)in persons 40-49 years

U.S. Preventive Services TASK FORCE **and** CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

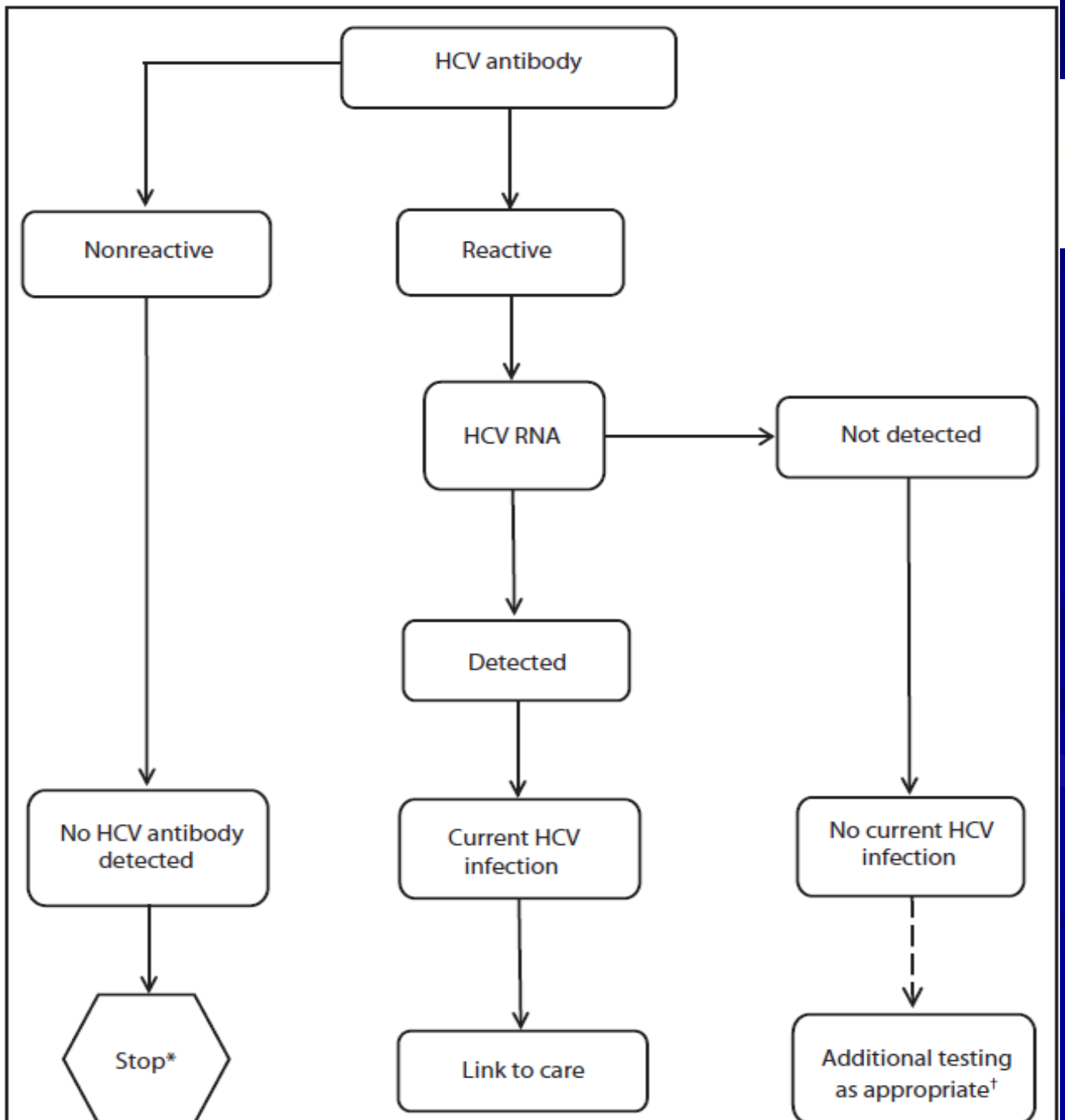
- Screen adults at risk for HCV infection PLUS
- Screen adults born 1945 through 1965
  - One-time testing for HCV without ascertainment of HCV risk factor

Smith BD et al. *MMWR Morb Mortal Wkly Rep*. 2012;61:1-32.

Recommended Testing Algorithm

- FDA-approved initial test for anti-HCV
  - Negative => can assume never infected
  - Positive => either
  - (i) has current HCV infection, or
  - (ii) had HCV infection in the past that has subsequently resolved (25%)
- Positive anti-HCV antibody MUST be followed by testing for HCV RNA quantitative analysis

FIGURE. Recommended testing sequence for identifying current hepatitis C virus (HCV) infection



MMWR / May 10, 2013

HCV Infection

• Incubation period	Average, 6–7 weeks
• Acute illness (jaundice)	Mild (20%–30%)
• Chronic hepatitis	70%
• Immunity	No protective antibody response identified

HCV has been classified into a total of six genotypes
75% of Americans with HCV have genotype 1

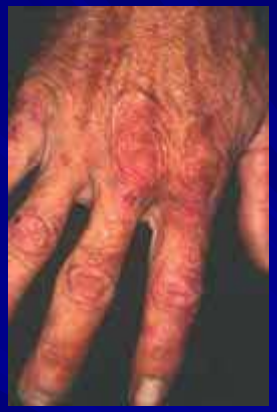
Risk factors for HCV infection

- Injection-drug use
- Intranasal illicit drug use
- Long-term hemodialysis (ever)
- Getting a tattoo in an unregulated setting
- Needle stick or mucosal exposures
- Children born to HCV-infected women
- Prior recipients of transfusions or organ transplants
- HIV infection
- Unexplained chronic hepatitis

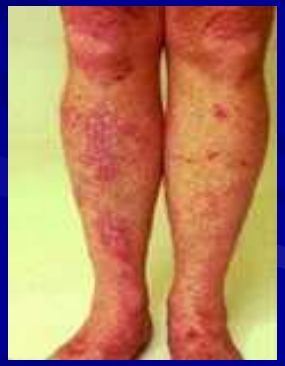
Extrahepatic Manifestations of Hepatitis C

- Insulin resistance (Diabetes)
- Strokes?
- Hematologic:
  - Mixed cryoglobulinemia

  (10%–25% of HCV patients)



- Renal: Glomerulonephritis
- B Cell Non hodgkins lymphoma
- Sjogren's syndrome
- Dermatologic:
  - Porphyria cutanea tarda
  - Cutaneous necrotizing vasculitis

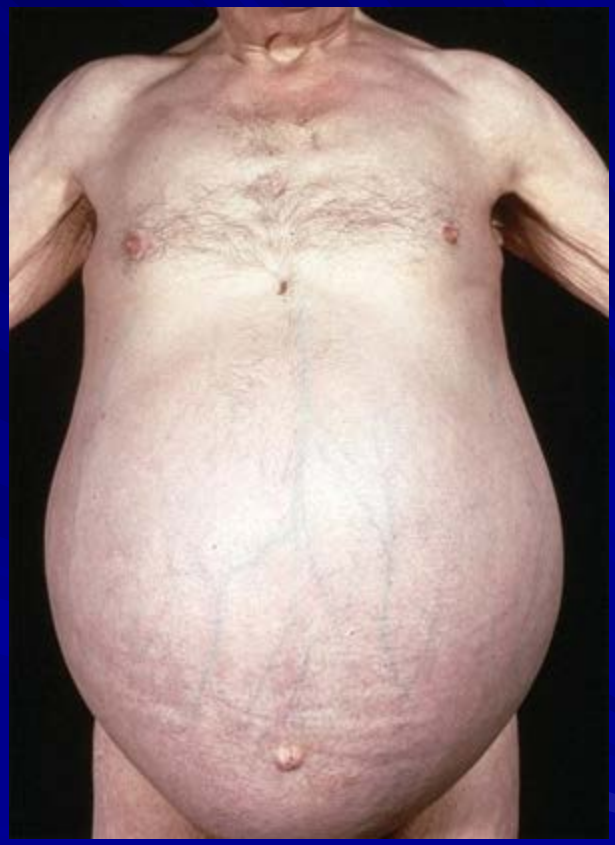


Management of Hepatitis C. NIH Consensus Statement, 2002.

Ascites is an ominous sign and is usually the first sign of liver decompensation

Other clues:

- Thrombocytopenia
- Anemia
- Hypoalbuminemia
- Coagulopathy
- Asterixis



Assessing Cirrhosis Severity: Child-Pugh Score

Variable Points	1	2	3
Encephalopathy grade	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Serum albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (sec prolonged)	< 4	4-6	> 6
Serum bilirubin (mg/dL)	< 2	2-3	> 3
Serum bilirubin if cholestatic disease (mg/dL)	(< 4)	(4-10)	(> 10)

- Child-Pugh A: 5-6 points
- Child-Pugh B: 7-9 points
- Child-Pugh C: ≥ 10 points

- Subjective component relies on clinical judgment

Pugh RN, et al. Br J Surg. 1973;60:646-649.

Case continued

Hepatitis C antibody positive, Genotype 1a HCV, HIV negative

- HCV RNA 5,400,000 IU/mL
- ALT 31 U/L

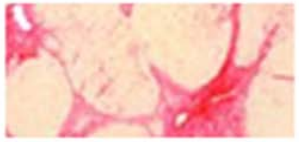
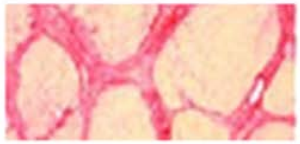
- What is the next step?
- 1. Start Hep C treatment
- 2. Assess extent of liver damage
- 3. Counsel and educate regarding treatment

Follow up on a positive HCV test

- Assess extent of liver damage : (Fibrosure®) OR Liver biopsy OR Fibroscan®
- Determine HCV genotype
  - to guide selection of the most appropriate antiviral regimen.
- Check LFT, (INR), CBC, HIV, Hep A, Hep B, alpha-fetoprotein
- Ultrasound liver
- Counsel and educate regarding treatment; abstinence from alcohol
- Vaccination against Hep A and Hep B

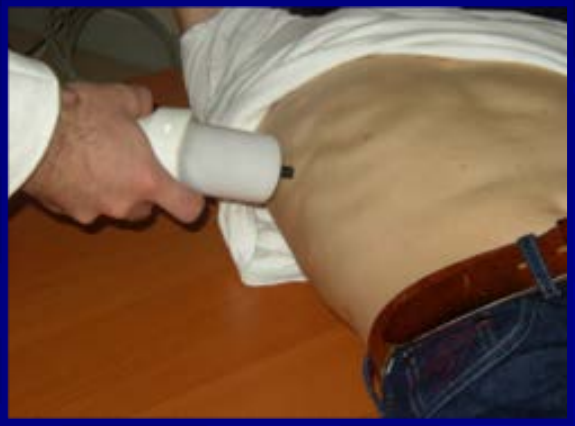
Staging liver disease

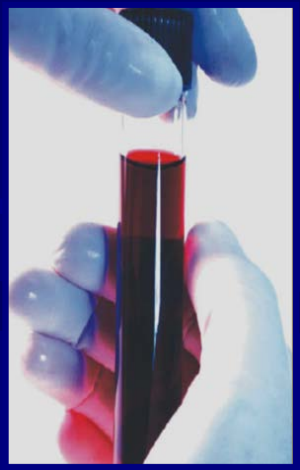
- Degree of inflammation
  - Disease severity
  - Tissue damage

Appearance	Ishak stage: Categorical description	ISHAK	METAVIR
	No fibrosis (Normal)	0	F0
	Fibrosis expansion of some portal areas ± short fibrous septa	1	F1
	Fibrosis expansion of most portal areas ± short fibrous septa	2	F2
	Fibrosis expansion of most portal areas with occasional portal to portal(P-P) bridging	3	
	Fibrosis expansion of portal areas with marked portal to portal(P-P) bridging as well as portal to central(P-C)	4	F3
	Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5	
	Cirrhosis, probable or definite	6	F4

Once diagnosed, providers have to prioritize based on Liver Fibrosis

Liver biopsy





Serum markers :

er Biopsy

HCV Fibrosure

HCV Fibrometer

FIB-4

APRI

Liver Elastography: A Fibroscan machine is needed and there are currently only 2 in the whole of South Carolina

FibroTest/Fibrosure

AUROC:
77-80%
for fibrosis

84%
for cirrhosis

Liver Fibrosis, FibroTest-ActiTest

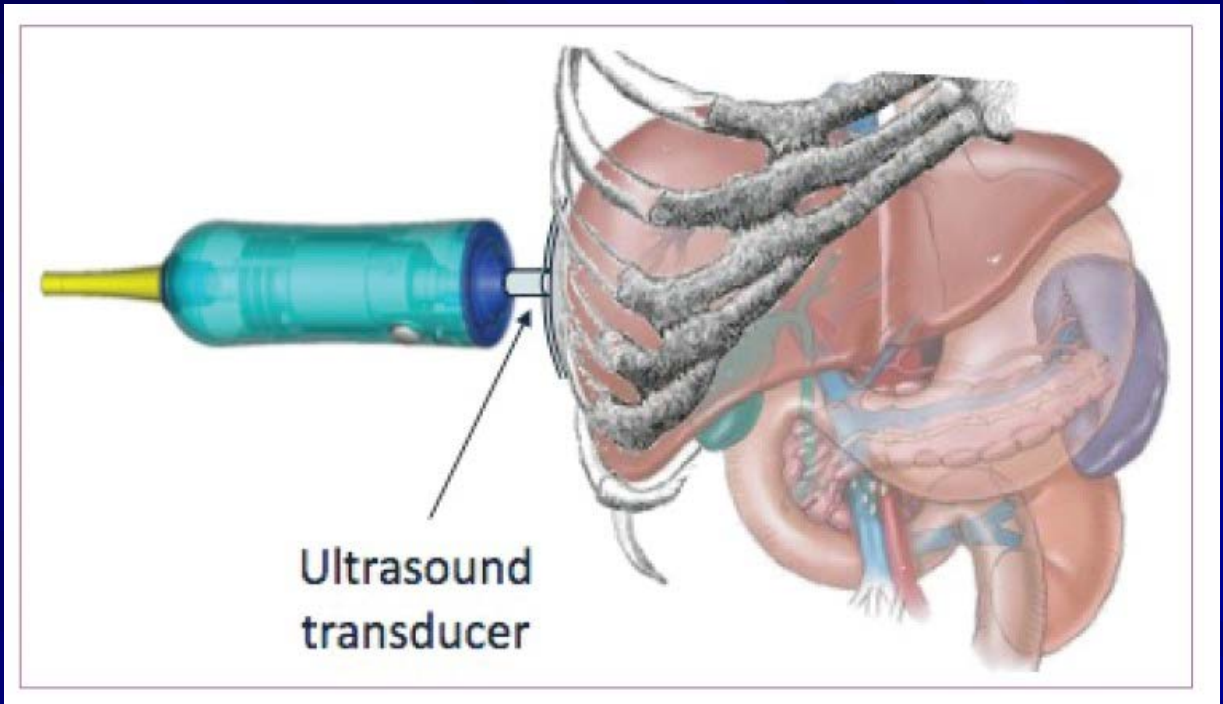
	NAME	VALUE	REFERENCE RANGE
F	Alpha-2-Macroglobulin	390 H	106-279 (mg/dL)
F	Haptoglobin	148	43-212 (mg/dL)
F	Apolipoprotein A1	116	94-176 (mg/dL)
F	Bilirubin	0.3	0.2-1.2 (mg/dL)
F	GGT	122 H	3-95 (U/L)
F	ALT	50 H	9-46 (U/L)
F	Fibrosis Score	0.64	
F	Fibrosis Stage	F3	
F	Fibrosis Interpretation	SEE NOTE	

-

- advanced fibrosis

-

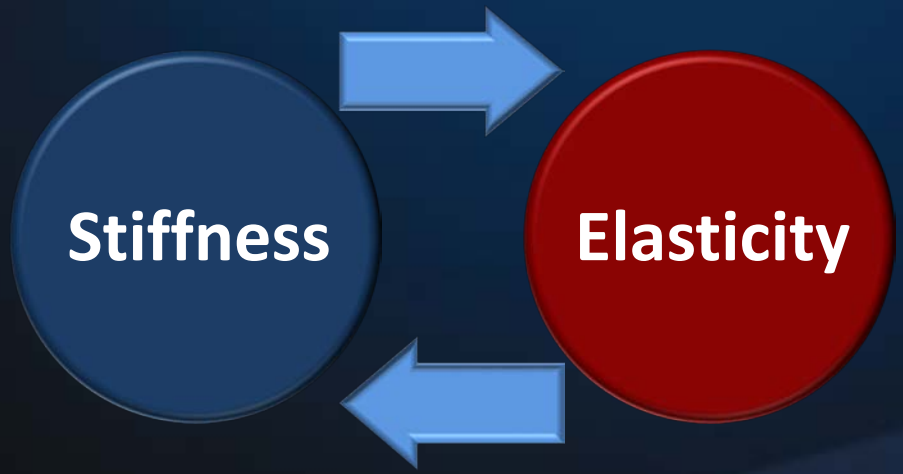
Fibroscan: Liver Elastography



- In April 2013, the FDA approved its use in the U.S.
- Between 90–95% of healthy people **without** liver disease will have a measurement< 7.0 kPa (median is 5.3 kPa).
  F2- 8kPa
- F4 > 12.9 kPa (>90% probability of having cirrhosis)

Noninvasive Liver Stiffness Testing

Assess mechanical properties of liver tissue



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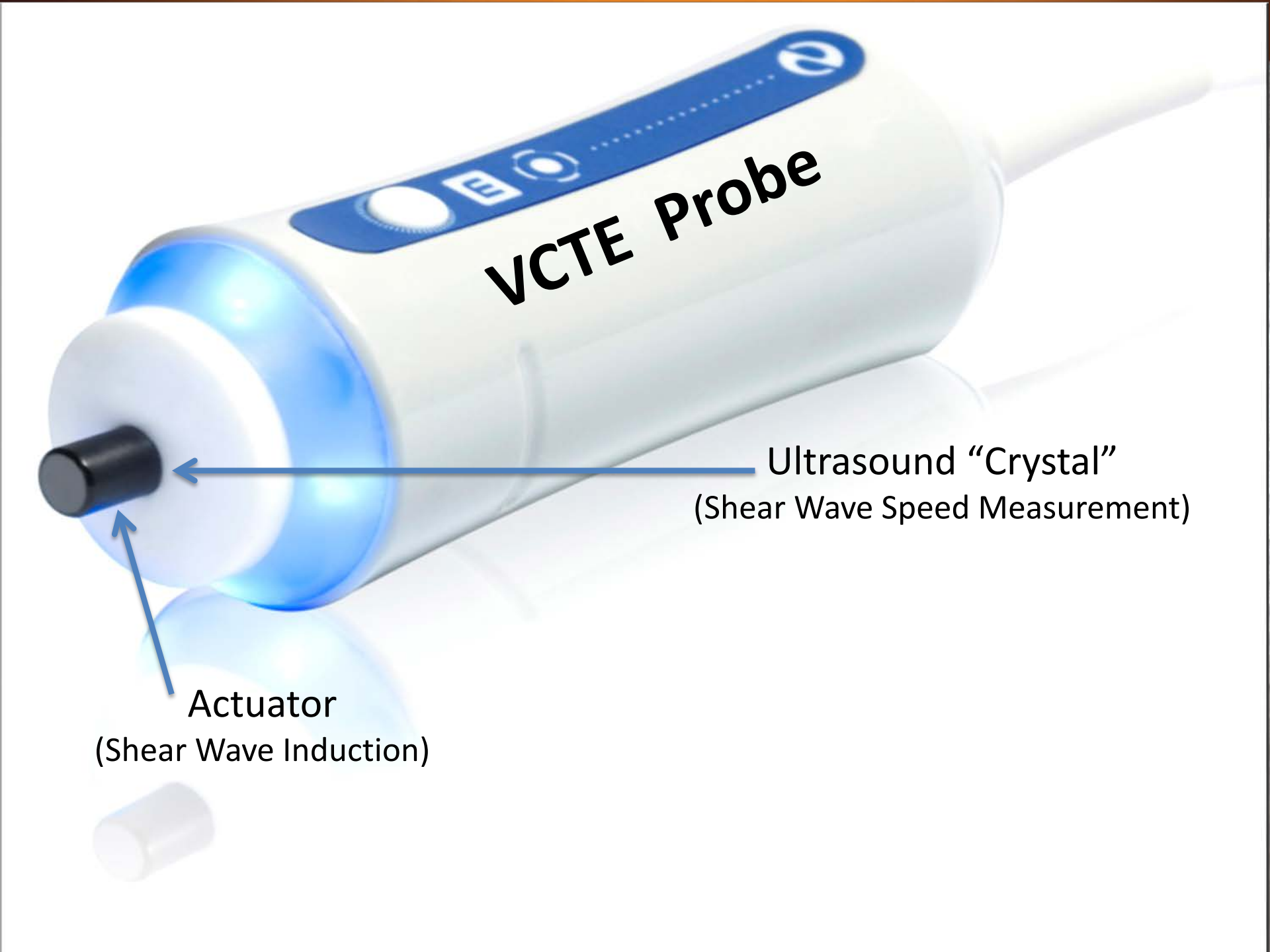
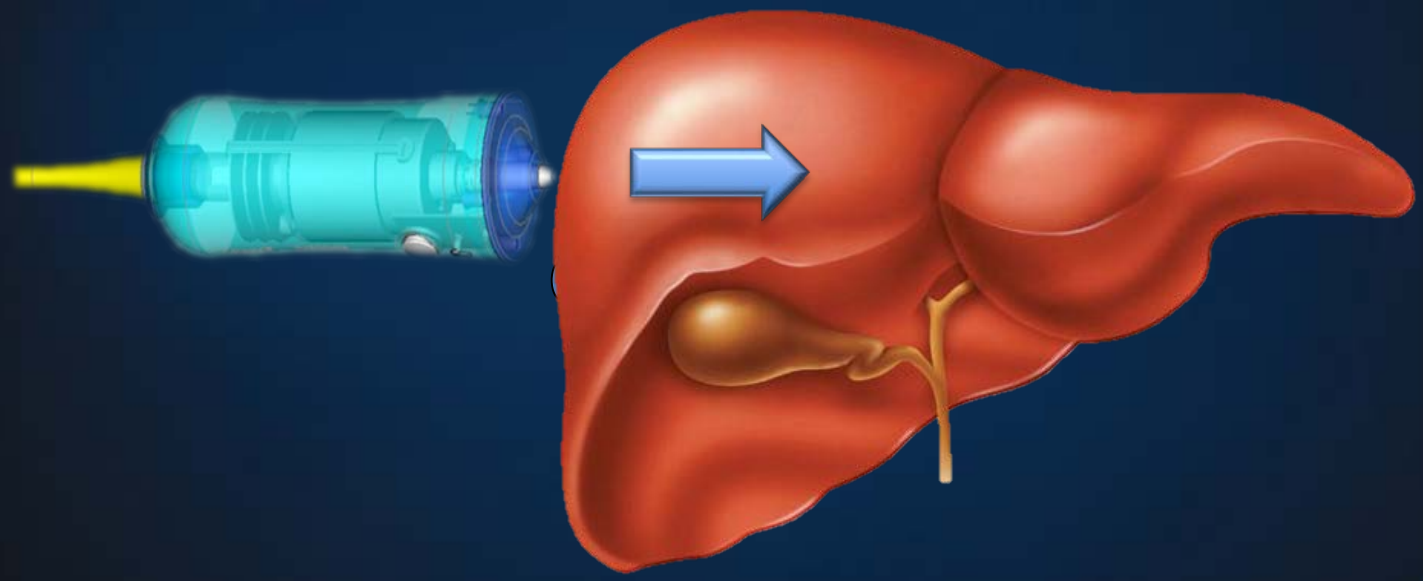
a medovations company


VCTE Probe
Ultrasound “Crystal”
(Shear Wave Speed Measurement)
Actuator
(Shear Wave Induction)

Mechanical Shear Wave Induction



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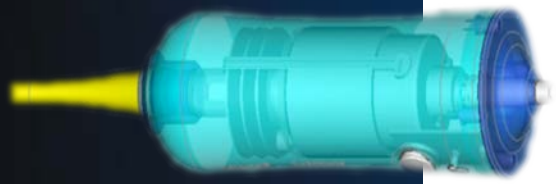
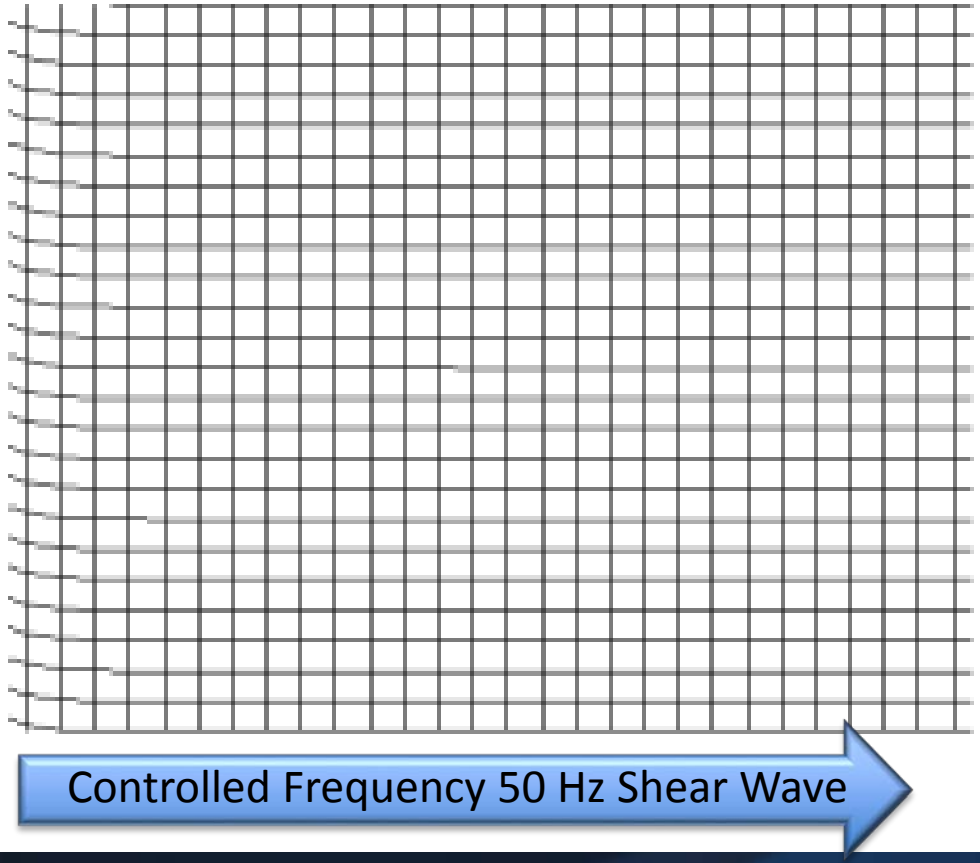
Shear Wave Movement





FibroScan Cutoff Value Reference

Multiple Disease Groups

Disease	F0-F1	F2	F3	F4
HBV	≤ 6.0	> 6.0	≥ 9.0	≥ 12.0
HCV	≤ 7.0	> 7.0	≥ 9.5	≥ 12.0
HCV-HIV	≤ 7.0	≤ 10.0	≥ 11.0	≥ 14.0
Cholestatic	≤ 7.0	≥ 7.5	≥ 10.0	≥ 17.0
NAFLD/NASH	≤ 7.0	≥ 7.5	≤ 10.0	≥ 14.0

Utilization of FibroScan in Clinical Practice; Current Gastroenterology Reports; Bonder & Afdahl; 2014; 16:372

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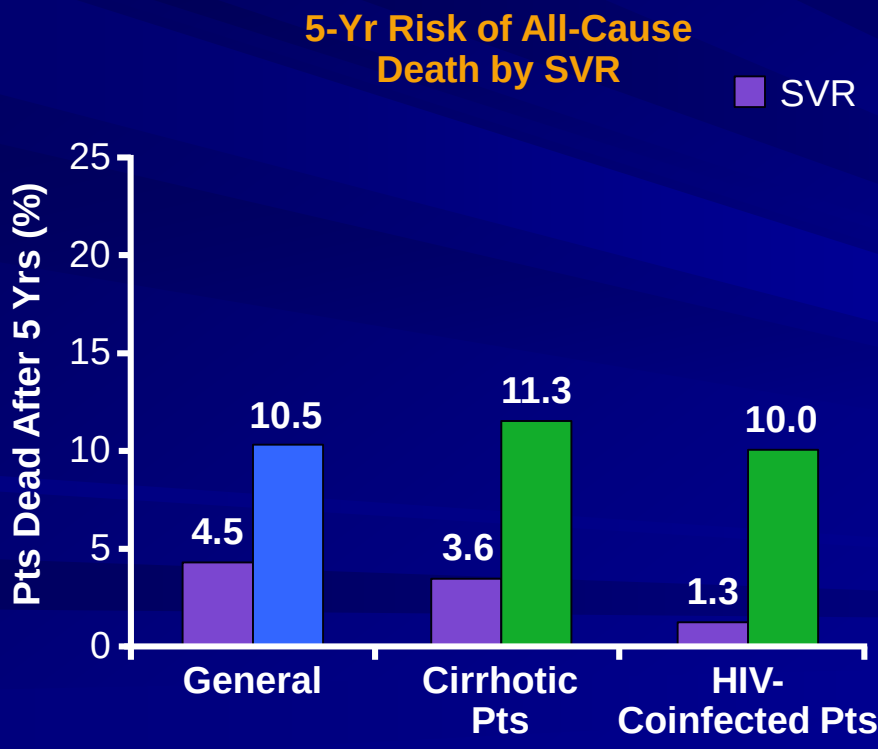
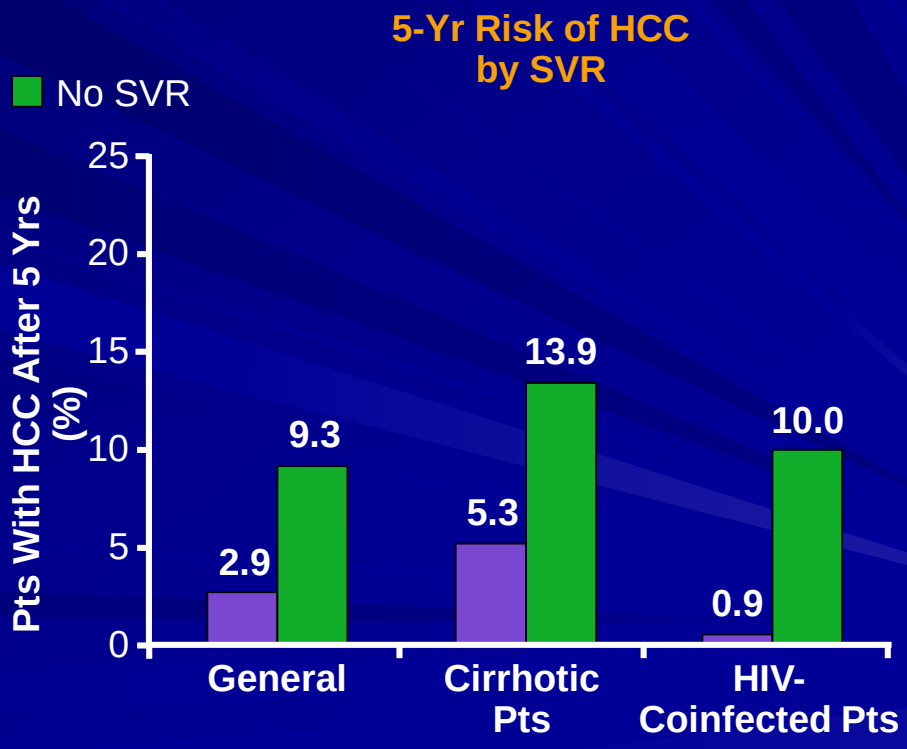
Patients with risk for complications

- Advanced fibrosis or compensated cirrhosis (≥ Metavir –F2-F3)
- Organ transplant
- Type 2 or 3 essential mixed cryoglobulinemia
- Membrano-proliferative glomerulonephritis
- HIV co-infection
- HBV co-infection
- Other coexistent liver disease
- Type 2 diabetes mellitus
- Porphyria cutanea tarda

SVR Associated With Reduced 5-Yr Risk of Death and HCC in All Populations

- SVR on IFN-based therapy was associated with substantial benefit vs no SVR
  - 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC





Hill AM, et al. AASLD 2014. Abstract 44.

Unlike HIV and HBV, HCV is curable

Virus	HIV	HBV	HCV
Genome	RNA	DNA	RNA
Mutation Rates	Very High	High	Very High
Virions Produced Daily	10^{10}	10^{13}	10^{12}
Long-lived proviral reservoir	YES	YES	NO
Viral Targets of Therapy	Multiple	One	Multiple
Cure With Current Therapy?	NO (Integrated viral DNA)	NO (cccDNA)	YES
Current Therapeutic Goal	Lifelong suppression	Lifelong suppression	**Cure** or eradication of HCV infection

Recommended assessments prior to starting antiviral therapy

- Assessment of potential drug-drug interactions
- Laboratory tests within 6 weeks prior to starting antiviral therapy:
  - CBC, INR, LFT, BMP
  - TSH, ANA; if IFN is used
  - Calculated glomerular filtration rate (GFR)
- Within 12 weeks prior to starting therapy:
  - HCV genotype and quantitative HCV viral load

Factors That Influence HCV Treatment Decisions

Category	Factors
Viral	▪ HCV GT ▪ Viral load
Treatment	▪ HCV treatment history – PegIFN + RBV – Protease inhibitor – Sofosbuvir ▪ RBV eligibility ▪ Resistance
Fibrosis stage	▪ Child-Pugh score ▪ If cirrhotic, any history of decompensation? ▪ Transplant evaluation if necessary
Coinfection/comorbidities	▪ HIV coinfection ▪ Cardiovascular, renal, metabolic, etc, concerns ▪ Drug–drug interactions
Financial	▪ Insurance approval

Slide credit: clinicaloptions.com

Oral Directly Acting Antivirals

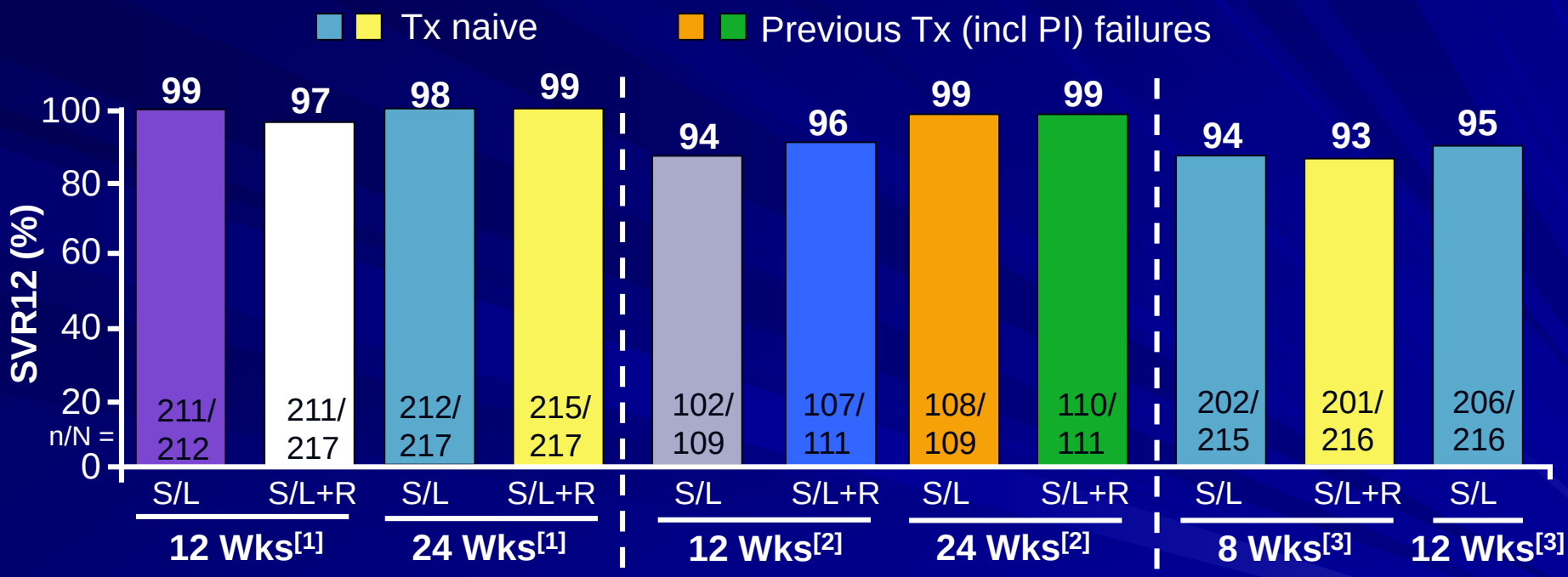
- Harvoni
- Viekira Pak
- Daclatasvir + Sofosbuvir
- Technivie
- Zepatier

Sofosbuvir/Ledipasvir
(Approved October 2014)

- Oral, once-daily fixed-dose combination of nucleotide NS5B polymerase inhibitor and NS5A inhibitor
- Combination has high barrier to resistance
- Pharmacology profile
  - Significant drug interactions include with P-gp inducers
- Approved for treatment of GT1 HCV
- Cost: $1125 per pill

Sofosbuvir/ledipasvir [package insert].

ION 1, 2, and 3: Sofosbuvir/Ledipasvir ± RBV in Tx-Naive Pts and Previous Failures



- 8 wks adequate for noncirrhotic treatment-naive pts
- RBV provides no benefit
- No SOF resistance observed; most virologic failures have LDV resistance

Baseline NS5A RAV: ION-1-16%,

AASLD Guidelines

Genotype 1 Treatment Naïve	Noncirrhotic Regimen	Duration (wks)	Compensated Cirrhotic Regimen	Duration (wks)
GT1a or 1b	LDV/SOF	12*	LDV/SOF	12
GT1a	OMV/PTV/RTV + DSV + RBV	12		
GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV	12
GT1a or 1b	SMV + SOF	12		
GT1a or 1b	DCV + SOF	12		
GT1a or 1b	EBR/GZR#	12	EBR/GZR#	12

*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider's discretion & with caution.

**Note: All Class IA recommendations except DCV + SOF is Class IB (no cirrhosis); Class IIaB (cirrhosis);

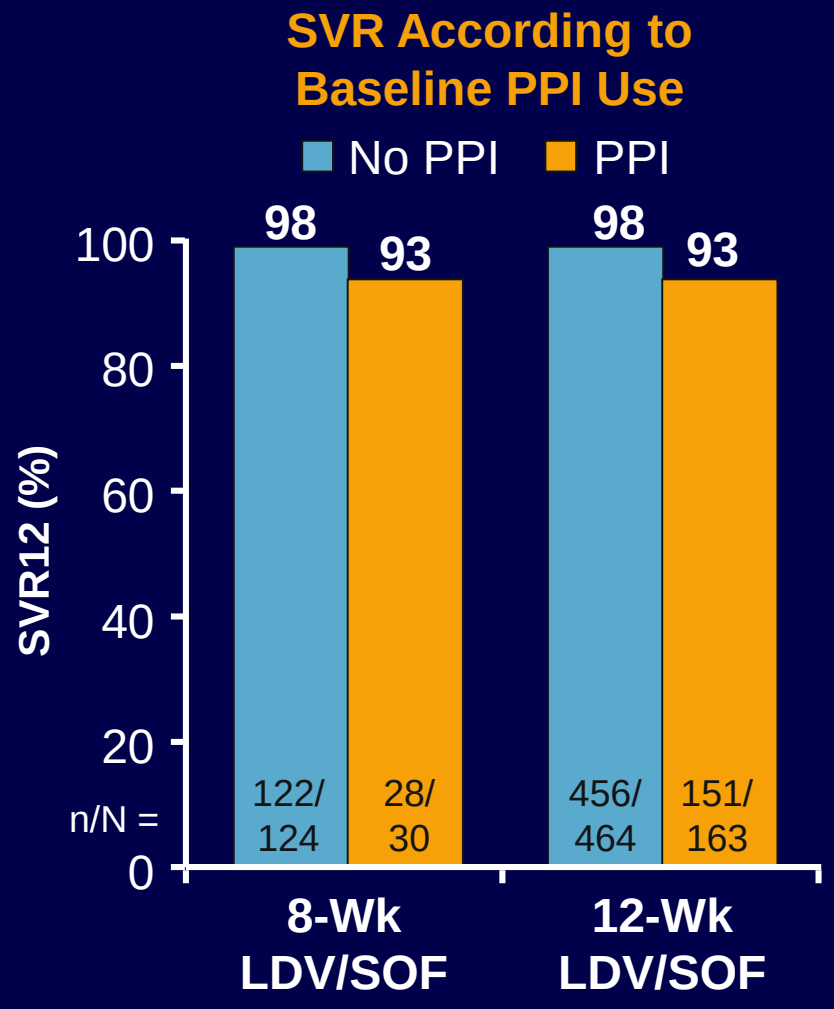
Must have no baseline high fold-change NS5A RAVs detected; only applicable to GT1a

Recommended monitoring during antiviral therapy

- Every 4weeks
  - CBC,BMP, calculated GFR, LFT.
  - Monitor CBC more closely if on RBV
- Quantitative HCV viral load testing
  - At 4 weeks
  - At the end of RX
  - 12 weeks after completion of therapy (and also 24 weeks after completion of therapy)

HCV-TARGET: Baseline Predictors of SVR in Pts Receiving Ledipasvir/Sofosbuvir

Baseline Predictor	OR (95% CI)	*P* Value
Albumin ≥ 3.5 g/dL	4.59 (2.06-9.85)	< .001
Platelet count, 1000/mm^3	1.01 (1.00-1.02)	< .001
Total bilirubin ≤ 1.2 mg/dL	3.65 (1.71-7.51)	.001
Hemoglobin, g/dL	1.22 (1.01-1.46)	.030
No cirrhosis	3.87 (1.91-8.23)	< .001
Compensated liver disease	5.49 (2.62-11.16)	< .001
No baseline PPI	3.02 (1.51-6.05)	.001



Terrault N, et al. AASLD 2015. Abstract 94. Reproduced with permission.

Resistance

- More commonly in genotype 1a vs 1b
- Q80K mutation (NS34A RAV)- 45% of US patients with genotype 1a HCV infection
- Baseline NS5A RAVs -16% with GT1
  - Have high viral fitness
  - Persist for up to 2 years
  - In GT 1a : NS5A RAVs result in a ≥ 100 fold resistance to these approved agents in vitro.

Acute HCV

- HCV infection will spontaneously clear in 20% to 30% of patients.
- In at two-thirds of patients, this will occur within 6 months
- Detectable HCV RNA at 6 months after the time of infection will identify most persons who need HCV therapy
- Predictors of spontaneous clearance include:
  - Jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, HCV genotype 1, and host genetic polymorphisms, most notably those near the IL28B gene.

CENTERS FOR DISEASE CONTROL AND PREVENTION

- **May 3, 2016**
- Acute cases of hepatitis C infection have more than doubled since 2010, increasing to 2,194 reported cases in 2014.
- The new cases were predominantly among young, white individuals with a history of injection drug use, living in rural and suburban areas of the Midwest and Eastern United States.

Review the approach to Hepatitis C

55 year male, intermittently elevated transaminases, Hepatitis C antibody positive.

What is the next step?

- See if he has Chronic HCV by checking his Quantitative RNA (Viral load), Check HIV
- Viral load is 1.2 million
- Next Step?

Follow up on a positive HCV test

- Assess extent of liver damage : (Fibrosure®) OR Liver biopsy OR Fibroscan®
- Determine HCV genotype
  - to guide selection of the most appropriate antiviral regimen.
- Check LFT, (INR), CBC, HIV, Hep A, Hep B, alpha-fetoprotein
- Ultrasound liver
- Counsel and educate regarding treatment; abstinence from alcohol
- Vaccination against Hep A and Hep B

- 55 y/o female treatment naïve Hepatitis C, GT 1b
- Home medications include:
  - Lisinopril 20mg daily/ HCTZ 12.5mg daily
  - Rosuvastatin 20mg daily
  - Omeprazole 40mg daily
- You want to initiate Harvoni® (sofosbuvir/ledipasvir)

Drug Interactions

Home Medications

Direct Acting Antiviral/Other Medication

- Rosuvastatin → ↑ ledipasvir exposure
  - Harvoni contraindicated
- Proton pump inhibitors → Antacids also decrease ledipasvir absorption

Karageorgopoulos DE.Curr Opin Infect Dis. 2014 Feb;27(1):36-45.
Harvoni (ledipasvir and sofosbuvir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; October 2014.

Hepatocellular Carcinoma (HCC)

- AASLD/IDSA HCV Guidance 2016
  - "Surveillance for HCC with twice-yearly ultrasound examination is recommended for pts with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve SVR"
- Main clinical prognostic factors
  - Tumor status (defined by number and size of nodules, presence of vascular invasion, extrahepatic spread)
  - Liver function (defined by Child–Pugh's class, bilirubin, albumin, portal hypertension, ascites)
  - Performance status

Hepatitis C

- >1% of the US population has Chronic Hepatitis C
- Interferon free, all–oral antivirals are well tolerated and have excellent cure rates (> 90%)
- SVR (cure) leads to a decrease in all cause mortality, liver decompensation and hepatocellular carcinoma
- Treatment regimens are very expensive and constantly evolving
- Primary care providers and their patients lack access to specialists

- **Goals of South Carolina Hepatitis C Telehealth Initiative**
  - Identify gaps and increase access to care for persons living with Chronic HCV, with emphasis on underserved and rural populations
  - CME accredited clinical training and case-based consultations via video conferencing for clinicians and other providers at FQHCs, Ryan White Clinics & AIDS Services Organizations
  - Reduce the morbidity, mortality and costs associated with advanced liver disease due to Hepatitis C