Hepatitis C QUIK FAQs

REFERENCE guide

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TRANSMISSION

- ► Efficiently transmitted via blood
  - • Viral titers often in the millions
  - • Durable ex-vivo – up to 4 days
- ► Injection drug users at high risk
  - • ~50% in 1st year
  - • ~70% after 5 years
- ► Small risk via non-injection drug use
  - • Drug straws and crack pipes may contain blood
  - • Behavioral risk with stimulant use
- ► Many infected via blood transfusion ≤1992
- ► Sexual transmission possible but uncommon
  - • ~2% of long term monogamous relationships
  - • Risk confined to first year
  - • Multiple partners/STD/HIV increase risk
  - • NOT by casual contact: hugging, kissing, eating and cooking utensils
- ► Breast feeding is safe
- ► Vertical transmission risk low, 5-6%
  - • C-section is not protective
- ► Lack of protective immunity: reinfection may occur
- ► Bleach kills HCV
  - • Difficult and impractical to decontaminate syringes
  - • Use only new equipment – needle exchanges, etc.

NATURAL HISTORY

- ► Benign in the majority of cases
  - • Only ~15% cirrhosis risk after 20 years
- ► Fibrosis risk increased by
  - • Alcohol
  - • Nicotine and cannabis, to a small extent
  - • Coinfections: HIV, HBV
- ► African-Americans less likely on average vs. Caucasians to develop cirrhosis
- ► Fibrosis progression dictated by host immune response
  - • HCV virus is not apoptotic
  - • Progression NOT related to viral load or genotype
  - • No need to perform serial viral loads
- ► ~25% clear virus spontaneously – it is GONE, not dormant
  - • Occurs within 6 months of initial exposure, if at all
  - • No risk for transmission to others
- ► ~75% develop chronic infection
  - • Presence of viremia ≥6 months after initial exposure
  - • Progression generally, but not always, slow

HCV TESTING

- **ALT/liver enzymes**: often normal
  - Screen based on risk factors and age, not labs
- **EIA screening test**: detects antibodies to HCV
  - Indicates prior exposure, NOT current infection
  - Screen all persons born between 1945-1965
  - Stays positive even after spontaneous clearance or treatment-related cure
  - Should be followed by reflex viral testing
- **RIBA**: outmoded and rarely needed
  - Differentiate false + Ab vs. spontaneous clearance
- **Viral testing**: required to diagnose current infection
  - Quantitative PCR: numbers typically in millions, or
  - Qualitative PCR/TMA: most sensitive assay, or
  - Genotype: 1-6, most common in U.S. is G1
    - Determines treatment duration, regimen, and success rate but NOT fibrosis progression
- **Liver imaging**: Ultrasound/CT of limited utility
  - Insensitive to fibrosis
- **Noninvasive fibrosis tests**: eg, Fibrosure, Fibroscan
  - Not FDA approved, less accurate than biopsy
  - Predict fibrosis via blood test panel or liver elasticity
- **Liver biopsy**: gold standard fibrosis quantification
  - Metavir stages 0-4, S4 = cirrhosis
  - Ischak stages 0-6, S6 = cirrhosis
- **IL28B genotype**: helps predicts treatment response
  - CC highly responsive vs. CT or TT

HCV TREATMENT-GENERAL CONSIDERATIONS

► Treatment algorithms are evolving rapidly and should be verified prior to initiating medications.

► The backbone of HCV treatment is pegylated interferon (PEG) and ribavirin (R) for all genotypes.

► Triple therapy with PEG/R and an HCV protease inhibitor (PI) is used for patients with genotype 1.

► Treatment duration is 24-48 weeks.

► The main determinant of treatment duration, regimen, and outcomes is the HCV genotype.

► **Genotype 1**: most common genotype in U.S. (75%) and least sensitive to interferon therapy. About 70% of patients treated for 24-48 weeks with PEG/R/PI triple therapy will have SVR.

► **Genotype 2**: the most interferon-sensitive genotype. About 85% SVR with 24 wks of PEG and ribavirin 400 mg bid.

► **Genotype 3**: less interferon sensitive than genotype 2. About 75% SVR with 24 wk PEG and ribavirin 400 bid. Consider 48 wk and ↑riba if no RVR.

► **Genotypes 4-6**: intermediate sensitivity. Treat for 48 wks with PEG/R.

TREATMENT CANDIDACY

► **Considerations:**

- Risk of progression to severe liver disease
- Probability of response
- Risk of adverse events
- Patient motivation

► **Indications:**

- Advancing/advanced fibrosis
- Compensated cirrhosis/bridging fibrosis
- Accelerated fibrosis: HIV/HCV or HBV/HCV coinfection
- Severe symptoms
- Extrahepatic disease; e.g., cryoglobulinemia
- Acute HCV

► **Contraindications:**

- Absolute:
  - Pregnancy
- Strong:
  - Hepatic decompensation
  - Solid organ transplant (except liver)
  - Severe heart/lung disease
- Relative
  - Autoimmune diseases
  - Unstable psychiatric disorder
  - Active alcohol/drug use

TREATMENT MEDICATIONS

► **Pegylated interferon**

- Currently the backbone of all treatment regimens
- Enhances innate immune response to HCV virus

► PEG= **P**oly**E**thylene **G**lycol, long chain carbohydrate that prolongs IFN half-life

► SQ injection once weekly

► Cytopenias, flu-like symptoms, fatigue, depression are major side effects

► **Ribavirin**

- Improves efficacy of interferon
- Oral agent
- No efficacy as monotherapy
- Can cause hemolytic anemia that may be severe

► **Protease inhibitors**: **Genotype 1 only**

- Telaprevir and boceprevir currently approved
- Used in combination with interferon and ribavirin
- High potential for resistance if not taken correctly
- Improve genotype 1 treatment outcomes by ~50%
- Boceprevir: fatigue, anemia, nausea, headache, dysgeusia
- Telaprevir: rash, itch, anemia, nausea, hemorrhoids, diarrhea, anorectal pain/itch, dysgeusia, fatigue, vomiting

HCV TREATMENT ABBREVIATIONS

	Term	Definition
RVR	Rapid virologic response	Undetectable HCV RNA at treatment week 4
EVR	Early virologic response	100-fold reduction or undetectable viral load at treatment week 12
cEVR	Complete early virologic response	Undetectable HCV PCR at treatment weeks 4 and 12
eRVR	Extended rapid virologic response	Undetectable HCV PCR at treatment weeks 4 and 12
ETR	End of treatment response	HCV PCR undetectable at end of treatment
SVR12	Sustained virologic response week 12	HCV PCR undetectable 12 weeks after end of treatment
SVR24	Sustained virologic response week 24	HCV PCR undetectable 24 weeks after end of treatment

HCV RESPONSE TERMS

Term	Defintion
Breakthrough	Reappearance of HCV RNA while on therapy
Non-response	Failure to clear HCV RNA by week 24
Null response	<100-fold drop in HCV RNA by week 12
Partial response	>100-fold drop in HCV RNA by week 12, but virus still detectable at week 24
Relapse	HCV PCR undetectable during treatment but positive afterward

HCV MEDICATION DOSING

► Pegylated Interferons

- **PEG IFN alfa-2a (Pegasys®)**: 180 mcg SQ/wk
- **PEG IFN alfa-2b (Peg-Intron®)**: dosed by weight:

Weight (in lbs)	Strength	Volume (cc/wk)
< 88#	50 mcg/0.5 cc	0.5 cc
88-111# 112-133#	80 mcg/0.5 cc	0.4 cc 0.5 cc
134-166# 167-186#	120 mcg/0.5 cc	0.4 cc 0.5 cc
188# and ↑	150 mcg/0.5cc	0.5 cc

HCV Medication Dosing (cont.)

► **Ribavirin :**

- Supplied as 200, 400, and 600 mg tabs/capsules
- Genotypes 2 and 3: 400 mg bid
- Other genotypes:

Weight (in lbs)	Daily dose
< 165#	400 mg qAM and 600 mg qPM
≥165-231#	600 mg bid
>231#	600 mg qAM and 800 mg qPM

► **Boceprevir (Victrelis®)**

- Genotype 1 only
- Taken in combo with interferon and ribavirin
- 800 mg (4 x 200 mg capsules) 3x daily (every 7-9 hours) with a meal or light snack
- Missed dose:
  - If < 2 hr before next dose, skip missed dose
  - If > 2 hr before next dose, take missed dose

► **Telaprevir (Incivek®)**

- Genotype 1 only
- Taken in combination with interferon and ribavirin
- 750 mg (2 x 375 mg tablets) 3x daily (every 7-9 hours) with ~20 grams of fat
- Missed dose:
  - If < 4 hr before next dose, skip missed dose
  - If > 4 hr before next dose, take missed dose

SAMPLE HCV BLOOD TESTING SCHEDULE

(Additional testing may be required based on treatment response)

	CMP	CBC	TSH	HCV PCR*
Baseline	x	x	x	x
Week 2	x	x		
Week 4	x	x		x
Week 8	x	x		x #
Week 12	x	x	x	x
Week 18	x	x		
Week 24	x	x	x	x
Week 30	x	x		
Week 36	x	x	x	
Week 42	x	x		
Week 48	x	x	x	x
Week 12 post-Tx	x	x	x	x
Week 12 post-Tx	x	x	x	x

Abbreviations: CMP, Comprehensive Metabolic Panel; CBC, Complete Blood Count; TSH, Thyroid Stimulating Hormone

* Viral loads should be tested with a sensitive assay such as TaqMan® with a lower limit of detection of ~10 IU/ml

Boceprevir-based treatment only

TREATMENT ALGORITHM: BOCEPREVIR

Treatment Duration:

- Cirrhosis and prior null responders: 48 weeks (4 wk P/R + 44 wk P/R/B)
- All others: Response-guided therapy based on HCV PCR (IU/ml) results:

Wk 4	Wk 8	Wk 12	Wk 24	Treatment Algorithm
< 0.5 log ↓				4 wk P/R + 44 wk P/R/B
	< 9.3	<100	<9.3	Naïve: 4 wk P/R + 24 wk P/R/B Experienced: 4 wk P/R + 32 wk P/R/B
	>9.3	<100	<9.3	4 wk P/R + 36 wk P/R/B + 12 wk P/R
		>100		STOP
			>9.3	STOP

(P=pegylated interferon; R=ribavirin; B=boceprevir)

TREATMENT ALGORITHM: TELAPREVIR

Treatment Duration:

- Prior null responders and partial responders: 48 weeks (12 wk P/R/T + 36 wk P/R)
- All others: Response-guided therapy based on HCV PCR (IU/ml) results:

Wk 4	Wk 12	Wk 24	Treatment Algorithm
<10	<10		12 wk P/R/T + 12 wk P/R
>10 ≤1000			12 wk P/R/T + 36 wk P/R
>1000			STOP
	>10 ≤1000		12 wk P/R/T + 36 wk P/R
	>1000		>1000
		>10	STOP

(P=pegylated interferon; R=ribavirin; T=telaprevir)

SIDE EFFECTS: GENERAL CONSIDERATIONS

- Every patient will have side effects! Management will improve adherence and outcomes.
- **Injection timing**: Side effects are often worse the day or two after IFN injection.
  - Take IFN before bedtime and before a day off.
  - PegIntron: take antipyretic 1 hr before injection.
  - Pegasys: take antipyretic 2 hr after injection.
- **Flu-like symptoms**: Increasing water intake to 3-4 liters daily (15-20 glasses) usually helps.
  - Sip from water bottle throughout the day.
  - Reduce intake in the evening to help with sleep.
  - Flavored waters are ok but sugared caffeinated beverages don't substitute.
- **Mood Changes**: Almost universal. Try to differentiate insomnia/exhaustion from incipient psychiatric disorders and intervene quickly – sedating antidepressants can be helpful.
- **Weight Loss**: Reduces treatment outcomes if severe. Encourage small, regular meals and eating favorite, high calorie foods.
- **Support network**: Supportive family and friends can make or break the treatment. Encourage family members to attend office visits.
- **Employment vs. Disability**: Focus, endurance, and mood will be impaired, but some find work distractions helpful. Make decisions based on type of work and medication tolerability.

SIDE EFFECTS: COMMON ISSUES

► **Hematologic:**

- **Hemolytic anemia:**
  - Test Hb bi-weekly or weekly if dropping rapidly.
  - If Hb <10, reduce ribavirin dose.
    - With Pegasys, reduce dose to 600 mg/d.
    - With PegIntron, reduce dose to 12 mg/kg/d, or 8 mg/kg/d if still low when rechecked.
  - If Hb < 8.5, discontinue ribavirin.
    - Restart riba at 600 mg/d; raising dose above 800 mg not recommended.
  - EPO unnecessary once virus is undetectable
    - If used, erythropoietin is dosed at 40K IU/wk and darbepoietin is dosed at100 mcg/wk.
  - PI dose reduction NOT recommended.
- **Neutropenia:**
  - Opinions on actionable threshold vary widely.
  - G-CSF used rarely except in cirrhotics.
  - African-Americans tend to have lower baseline ANC and may reach action thresholds earlier.
  - General recommendations: ANC <750, ↓IFN by 25-50%; ANC <500, d/c IFN until ANC >1000.
- **Thrombocytopenia:**
  - General recommendations: if platelets are <50K, reduce IFN by 50%, if platelets are <25K, d/c IFN.
  - Management strategies vary widely.

SIDE EFFECTS: COMMON ISSUES

► **Systemic**:

- **Nausea/vomiting/weight loss**: Try split-dosing ribavirin to tid or qid. Antiemetics such as prochlorperazine or promethazine, hydroxyzine, H2 blockers, or PPIs can help.
- **Diarrhea**: Clear liquids, avoid milk products; Imodium or loperamide may help.
- **Dysgeusia**: May benefit from foods that are cold, aromatic, or acidic; ginger; dark chocolate. Possible benefit from zinc sulfate, 220 mg bid.
- **Anorectal pain**: Can be severe with telaprevir. Assess fat intake: ensure high fat meal and no medication interactions. Try local agents like Prep-H or Anusol ± hydrocortisone.

► **Dermatologic**

- **Rash/Itch:** Lightly coat skin with sealing emollients like Vaseline after bathing. Steroid ointments and oral antihistamines like Benadryl or hydroxyzine may be useful. Telaprevir can cause a severe rash requiring treatment discontinuation.
- **Injection site reactions**: Change injection site weekly to minimize risk for local inflammation.
- **Alopecia**: Will not be complete and hair will regrow. Reassurance is mostly needed; gentle treatment of hair and scalp will minimize impact.

► Neuropsychiatric

- Insomnia:
  - Assess sleep hygiene, caffeine, nicotine.
  - Don't take ribavirin at bedtime.
  - Start with sedating antihistamines or low dose sedating antidepressants like amitriptyline 25-50 mg qhs, trazodone 50-100 mg qhs, mirtazapine 15 mg qhs.
  - Use sedatives like zolpidem or short-acting benzos with care.
  - If on PI, check for drug-drug interactions.
- **Depression**:
  - Consider pre-treating persons with psych history.
  - Assess for and treat insomnia.
  - SSRI's considered first line agents, individualize treatment based on side effect profile (e.g., activating antidepressant if fatigue is problematic).
  - If on PI, check for drug-drug interactions.
- **Mood instability**: May be severe.
  - Assess for insomnia and depression/mania.
  - Mood stabilizing antipsychotics such as quetiapine or aripiprazole can help.
  - If on PI, check for drug-drug interactions.

HELPFUL REFERENCES

AASLD Practice Guidelines: Free availability online.

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- Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49(4):1335-1374.

Clinical Studies:

- Poordad F, et al. Boceprevir for untreated chronic HCV Genotype 1 infection. N Engl J Med 2011;364(13):1195-1205.
- Bacon BR, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364(13):1207-1217.
- Jacobson IM, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364(25):2405-2416.
- Zeuzem S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364(25):2417-2428.

Websites:

- **CDC Viral Hepatitis Section**: www.cdc.gov/ncidod/diseases/hepatitis
- **Veterans Affairs:** www.hepatitis.va.gov
- **HCV Advocate**: www.hcvadvocate.org. Packed with information about viral hepatitis.
- **Hepatitis Central**: www.hepatitis-central.com. Research & treatment news.

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