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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
  • Ishak 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= PolyEthylene Glycol**, 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
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR</td>
<td>Rapid virologic response</td>
</tr>
<tr>
<td></td>
<td>Undetectable HCV RNA at treatment week 4</td>
</tr>
<tr>
<td>EVR</td>
<td>Early virologic response</td>
</tr>
<tr>
<td></td>
<td>100-fold reduction or undetectable viral load at treatment week 12</td>
</tr>
<tr>
<td>cEVR</td>
<td>Complete early virologic response</td>
</tr>
<tr>
<td></td>
<td>Undetectable HCV PCR at treatment weeks 4 and 12</td>
</tr>
<tr>
<td>eRVR</td>
<td>Extended rapid virologic response</td>
</tr>
<tr>
<td></td>
<td>Undetectable HCV PCR at treatment weeks 4 and 12</td>
</tr>
<tr>
<td>ETR</td>
<td>End of treatment response</td>
</tr>
<tr>
<td></td>
<td>HCV PCR undetectable at end of treatment</td>
</tr>
<tr>
<td>SVR12</td>
<td>Sustained virologic response week 12</td>
</tr>
<tr>
<td></td>
<td>HCV PCR undetectable 12 weeks after end of treatment</td>
</tr>
<tr>
<td>SVR24</td>
<td>Sustained virologic response week 24</td>
</tr>
<tr>
<td></td>
<td>HCV PCR undetectable 24 weeks after end of treatment</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Reappearance of HCV RNA while on therapy</td>
</tr>
<tr>
<td>Non-response</td>
<td>Failure to clear HCV RNA by week 24</td>
</tr>
<tr>
<td>Null response</td>
<td>&lt;100-fold drop in HCV RNA by week 12</td>
</tr>
<tr>
<td>Partial response</td>
<td>&gt;100-fold drop in HCV RNA by week 12, but virus still detectable at week 24</td>
</tr>
<tr>
<td>Relapse</td>
<td>HCV PCR undetectable during treatment but positive afterward</td>
</tr>
</tbody>
</table>

**HCV MEDICATION DOSING**

► Pegylated Interferons

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

<table>
<thead>
<tr>
<th>Weight (in lbs)</th>
<th>Strength</th>
<th>Volume (cc/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 88#</td>
<td>50 mcg/0.5 cc</td>
<td>0.5 cc</td>
</tr>
<tr>
<td>88-111#</td>
<td>80 mcg/0.5 cc</td>
<td>0.4 cc</td>
</tr>
<tr>
<td>112-133#</td>
<td>80 mcg/0.5 cc</td>
<td>0.5 cc</td>
</tr>
<tr>
<td>134-166#</td>
<td>120 mcg/0.5 cc</td>
<td>0.4 cc</td>
</tr>
<tr>
<td>167-186#</td>
<td>120 mcg/0.5 cc</td>
<td>0.5 cc</td>
</tr>
<tr>
<td>188# and ↑</td>
<td>150 mcg/0.5 cc</td>
<td>0.5 cc</td>
</tr>
</tbody>
</table>
HCV Medication Dosing (cont.)

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

<table>
<thead>
<tr>
<th>Weight (in lbs)</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 165#</td>
<td>400 mg qAM and 600 mg qPM</td>
</tr>
<tr>
<td>≥165-231#</td>
<td>600 mg bid</td>
</tr>
<tr>
<td>&gt;231#</td>
<td>600 mg qAM and 800 mg qPM</td>
</tr>
</tbody>
</table>

► 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)

<table>
<thead>
<tr>
<th></th>
<th>CMP</th>
<th>CBC</th>
<th>TSH</th>
<th>HCV PCR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Week 2</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Week 8</td>
<td></td>
<td>x</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td>x</td>
<td></td>
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</tr>
<tr>
<td>Week 18</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 30</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 36</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12 post-Tx</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12 post-Tx</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Wk 4</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>Treatment Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5 log ↓</td>
<td></td>
<td></td>
<td></td>
<td>4 wk P/R + 44 wk P/R/B</td>
</tr>
<tr>
<td>&lt; 9.3</td>
<td>&lt;100</td>
<td>&lt;9.3</td>
<td></td>
<td>Naïve: 4 wk P/R + 24 wk P/R/B Experienced: 4 wk P/R + 32 wk P/R/B</td>
</tr>
<tr>
<td>&gt;9.3</td>
<td>&lt;100</td>
<td>&lt;9.3</td>
<td></td>
<td>4 wk P/R + 36 wk P/R/B + 12 wk P/R</td>
</tr>
<tr>
<td>&gt;100</td>
<td></td>
<td></td>
<td>STOP</td>
<td></td>
</tr>
<tr>
<td>&gt;9.3</td>
<td></td>
<td></td>
<td>STOP</td>
<td></td>
</tr>
</tbody>
</table>

(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:

<table>
<thead>
<tr>
<th>Wk 4</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>Treatment Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>&lt;10</td>
<td></td>
<td>12 wk P/R/T + 12 wk P/R</td>
</tr>
<tr>
<td>&gt;10 ≤1000</td>
<td></td>
<td></td>
<td>12 wk P/R/T + 36 wk P/R</td>
</tr>
<tr>
<td>&gt;1000</td>
<td></td>
<td></td>
<td>STOP</td>
</tr>
<tr>
<td>&gt;10 ≤1000</td>
<td>&lt;10</td>
<td></td>
<td>12 wk P/R/T + 36 wk P/R</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>&gt;10</td>
<td></td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>&gt;1000</td>
<td>STOP</td>
</tr>
</tbody>
</table>

(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 at 100 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.
SIDE EFFECTS: COMMON ISSUES

► 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.


Clinical Studies:


Websites:

• CDC Viral Hepatitis Section: www.cdc.gov/ncidod/diseases/hepatitis
• Veterans Affairs: www.hepatitis.va.gov