A Guide to Pre–treatment Evaluation
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ACG's Hepatitis School
Hepatitis C: A Guide to Pre–Treatment Evaluation
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The Future of Hepatitis C Therapy
(with apologies to Bob Dylan)

"The line it is drawn
The curse it is cast
The slow one now
Will later be fast
As the present now
Will later be past
The order is
Rapidly fadin'
And the first one now
Will later be last
For the times they are a-changin' "
Treatment of Hepatitis C

**Decision points:**
- Which patients to treat now with BOC or TVP regimens
- Which patients to treat with Peg + Riba
- Which patients to “warehouse” awaiting new DAAs or interferon/ribavirin–free regimens
- Which patients to refer for transplant

HCV: Patent Selection and Pre–treatment Assessment

**Factors to consider:**
- Acute vs chronic HCV
- Compensated vs. Decompensated HCV
- Contraindications to interferon, ribavirin, DAAs
  - Absolute
  - Relative
- Viral factors (genotypes)
- Host factors, co–morbidities
- Substance abuse
- Potential for drug–drug interactions and polypharmacy
- Patient motivation, compliance, support systems
Acute HCV – Factors to Consider

- Most cases stem from IVDU
- Spontaneous clearance in up to 50% of symptomatic patients
- Asymptomatic patients do not have spontaneous clearance
- Spontaneous clearance associated with IL28B CC (64%) vs 24% (CT) and 6% (TT) [Tillmann 2010]
- Antiviral Tx reduces risk of chronic HCV by 49% (CI 33–65%) [Licata 2003]
- SVR with standard IFN alfa monotherapy 83–100%; similar SVR with Peg–IFN
- Ribavirin does not lead to higher SVR in acute HCV

Acute Hepatitis C – Treatment Guidelines

**AASLD guidelines:**
- IFN–based Tx (including Peg–IFN) can be considered
- Tx can be delayed for 8–12 wks to allow for spontaneous clearance
- Ideal duration of Tx unknown – minimum 12 wks

**EASL guidelines:**
- 24 wks Peg monotherapy at standard doses
- Ribavirin can be added where diagnosis of acute vs chronic is uncertain
Acute HCV – How To Treat?

- “Asymptomatic” acute infections should receive Tx at the time of Dx
- “Symptomatic” patients who fail to clear the virus by 12 weeks should be treated
- IL28-B T/T (or C/T) are less likely to clear and should be treated
- SVR rates highest when treatment initiated within 48 wks of acute Dx for all IL28-B genotypes (compared to after 48 wks: CC = 69%, CT = 86%, TT = 0%) [Mangla 2011]
- Peg–IFN (dose >1.2ug/kg/wk) effective and simpler to use than non–Peg

Acute Hepatitis C is relatively easy: What about Chronic HCV?

- Pre–treatment evaluation to determine eligibility for therapy or contraindications
  1. History
  2. Physical exam
  3. Psychological screening
  4. Alcohol and other life–style issues
  5. Laboratory testing
  6. Need for liver biopsy
  7. Miscellaneous evaluations
Pretreatment evaluation of HCV: Medical History

- **Cardiac disease** (coronary events, CABG, exercise tolerance, risk factors [DM, HTN, Lipids, Fam Hx], results of echo, stress test, cardiac cath, etc)
- **Psychosocial** (substance abuse, mood disorders, depression, use of antidepressants and psychotropics)
- **Thyroid disease**
- **Extrahepatic manifestations** of HCV (PCT, B-cell lymphoma, glomerular disease, cryoglobulinemia, etc)
- **Autoimmune diseases**, psoriasis, sarcoidosis, AIH

How much alcohol is too much?

*My Doctor said "Only 1 glass of alcohol a day". I can live with that.*
Pretreatment evaluation of HCV: Physical Exam

Assess for presence of cirrhosis/decompensation/Tx contraindications

- General appearance
- Cutaneous lesions, rash, spider angioma, palmar erythema (other findings of cirrhosis)
- Scleral icterus, retinopathy
- Thyroid lesions
- Cardiac/valvular disease
- COPD
- Gynecomastia
- Organomegaly, umbilical hernia, ascites
- Peripheral edema, muscle wasting
- Asterixis, orientation, level of awareness

Pretreatment evaluation of HCV: Lab Assessment

- Viral load (to confirm infection)
- Genotype/ IL28–B polymorphisms
- CBC, platelets
- Synthetic function – INR, alb/glob, bili
- MELD score
- AST:ALT ratio
- TSH
- HIV
- Autoantibodies (ANA, ASMA, etc)
- Pregnancy testing
PreTreatment evaluation of HCV: Miscellaneous

- Formal ophthalmologic exam prior to interferon
- Checking immunity for hepatitis A and B and offering vaccination
- Offering vaccination for influenza, pneumococcus, varicella–Zoster, etc
- Primary and secondary prophylactic of large varices in decompensated pts

PreTreatment evaluation of HCV: Liver Biopsy: is it still needed?

- Biopsy still considered the “gold standard” *(but we went off the Gold Standard in 1971!)*
- The degree of fibrosis, presence of cirrhosis have a large impact on treatment decisions, duration of Tx, etc.
- Only liver biopsy can confidently exclude other liver disorders (AIH, iron overload, NASH, ALD)
- Clinical trials required histology as a clinical improvement endpoint
- Most gastroenterologists (and many hepatologists) no longer want to perform liver biopsies themselves (let the Radiologist do it!)
PreTreatment evaluation of HCV: 
Liver Biopsy: can we do without it?

- **Non-invasive markers of fibrosis:**
  - collagen markers (FibroSure, FibroSpect)
  - devices (elastography by FibroScan)
  - APRI: AST:platelet ratio index
  - imaging (US, MRI,CT)

- Sensitivity and specificity of FibroSure is about 80% – better at the extremes (but over- and under-estimations are common)
- Sensitivity and specificity of Fibroscan are 87% and 91% (but technical limitations include obesity, heart failure)

Eligibility for HCV Tx with Peg and Ribavirin

- Various prospective and retrospective studies have deemed many patients with chronic HCV ineligible for Tx:
  - 68% in VAMC study [Bini et al AJG 2005;100:1772]
  - only 12% were treated in another VA study [Butt et al Gut 2007;56:385]
  - 30% of 1337 excluded from a registration trial [McHutchinson et al NEJM 1998;339:1485]
  - 72% of 293 at Cleveland Clinic [Falck-Ytter et al Ann Intern Med 2002;136:288]
Contraindications to Peg and Riba in the general population of the US

- **GE Centricity HER dataset** of nearly 22 million persons contained 45,690 with HCV+ between 2004–2009 eligible for study
- 17.3% were ineligible for Tx using a set of standard contraindications
- 1.9% had two contraindications
- 0.3% had 3 contraindications
- <0.1% had >3 contraindications


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Contraindications in the Centricity Dataset

- Bipolar disorder 6.5% of the pop (37.6% of all contraindications); Hx suicide n=1
- Hemoglobin <10g 5.9% (34.1%)
- Neutrophils <750 1.2%
- Hepatic decompensation 1.2%
- Platelets <50,000 1.1%
- Acute MI or ACS 0.6%/0.1%
- Pregnancy 0.6%
- Renal transplant 0.3%
- Hemoglobinopathies 0.2%
- Uncontrolled seizures 0.1%
- Allergy to IFN or riba 0.1%
- Retinopathy n=1

*Talal et al APT 2013
Psychiatric Comorbidities in HCV Patients

- HCV infection ~ 11 times more prevalent among patients with psychiatric disorders vs general population in US and abroad
- Several psychiatric comorbidities in HCV
  - Depression rates between 25% and 34% in major HCV trials
  - Depression, anxiety, mood disorders can intensify over time
  - Cognitive impairment (Brain fog), agitation, irritability, insomnia, mania, hypomania are common
  - Depression is the leading cause of treatment non-adherence and can lead to discontinuation
  - Acute psychoses, suicidal ideation and suicide attempts in 2% during initial drug approval

Approach to Managing Psychiatric Issues During HCV Treatment

**Education, monitoring, and support**
- Consider standardized screening tools (CES-D, Center for Epidemiologic Studies Depression Scale; BDI, Beck Depression Inventory, etc)
- Information and psychoeducation before and during treatment
- Monitoring of patients and psychiatric issues
- Supportive psychotherapy; educate family members
- Regulation of sleep

**Pharmaceutical strategies**
- Antidepressants
- Other treatments: antipsychotics, anxiolytics, mood stabilizers, tryptophan, etc
- Antiviral therapy dose reduction, discontinuation

**Multidisciplinary approach** - including psychiatrist and psychotherapist
Traditionally Hard to Treat HCV Patients

- Older age (longer duration of infection)
- African American, Hispanic race
- High viral load
- Genotypes 1, 4
- IL28–B non–CC
- Advanced fibrosis, cirrhosis
- Former null responders
- Insulin resistance, obesity

Other HCV Patient Factors to Consider with DAAs

- Degree of polypharmacy
- Drugs interacting with CYP3A4 enzymes
- Co–morbidities
Co–Morbidity and RVR

- **Charlson Co–morbidity Index**
  - predicts 10–year mortality based on the risk of dying associated with various conditions
  - conditions assigned scores of 1, 2, 3 or 6
- Most common comorbidities in the first 74 patients treated with DAAs at MGUH:
  - diabetes 15%, PUD 11%, COPD 9.5%, Hx malignancy 8%, CNS dis 5.4%, CHF 4%, CRF 4%, CAD 3%
- Mean CCI 2.27 (1.9 in men, 2.82 in women; 2.41 for AAs, 2.23 for Caucasians)

*Juneja M, et al MGUH (DDW 2013 poster presentation)*

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Co–Morbidity and RVR

- Strong correlation between CCI and number of medications taken
- Patients achieving RVR and eRVR had a lower CCI compared to those not achieving viral undetectability (1.61 vs 2.8, p<0.02)

*Juneja M, et al MGUH (DDW 2013 poster)*
Polypharmacy and RVR

- Minor polypharmacy: 2–4 medications
- Major polypharmacy: 5 or more medications
- # meds (prescription and OTC) taken by first 74 genotype 1 HCV patients treated with DAAs at MGUH was 7.35 (+/- 3.7)
  - women 8.6 vs 6.6 for men (p<0.02)
- Patients achieving RVR and eRVR took a mean of 5 meds vs 9.24 for those not having viral undetectability (p <0.005)
- 91% with minor polypharmacy achieved RVR and eRVR vs 25% with major polypharmacy (p<0.005)

Juneja M, et al MGUH (DDW 2013 poster presentation)
PreTreatment evaluation of HCV: Checking for Drug–Drug Interactions

**CYP3A4/5-dependent drugs contraindicated with PIs due to increased serum concentrations and potential for adverse events:**

- alpha 1-adrenoreceptor antagonist (Alfuzosin) – hypotension
- Ergot derivatives (ergotamine) – vasospasm
- Cisapride – cardiac arrhythmias
- Statins (lovastatin, simvastatin) – rhabdomyolysis
- Oral contraceptives (estradiol, progestins) – unwanted pregnancy
- PDE5 enzyme inhibitors (sildenafil, tadalafil for PA hypertension) – hypotension, priapism
- Cardiovascular (amiodarone, bosentan, flecanide, quinidine, lidocaine) – cardiac arrhythmias
- Sedative/hypnotics (triazolam, oral midazolam) – increased sedation, respiratory depression

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PreTreatment evaluation of HCV: Checking for Drug–Drug Interactions

- **CYP3A4/5 inducers contraindicated with PIs due to decreased serum concentrations of the PI and loss of virologic response:**
  - Anticonvulsants (carbamazepine, phenobarbital, phenytoin)
  - Antimycobacterials (rifampicin)
  - Herbals (St John’s wort)
DDIs with HCV PIs: Use with caution

- Digoxin (selective substrate of P-gp) needs lower doses
- Antifungals (ketoconazole, itraconazole, voriconazole)
- Calcium channel blockers, ARBs
- Statins (pravastatin, rosuvastatin, atorvastatin)
- Respiratory (Salmeterol, fluticasone)
- Benzos (Trazadone, alprazolam)

*Kiser et al. Hepatology 2012;55:1620*

DDIs: Immunosuppressants, HAART and DAAs (TPV, BOC)

- Cyclosporine: AUC increased 2.7X, 4.6X
- Tacrolimus: AUC increased 70X, 17X
- PK of TPV, BOC not affected by cyclosporine or tacrolimus; nor by tenofovir
- Tenofovir Cmax increased 30% with both
- TVP, BOC Cmax reduced by efavirenz
- Ritonavir used to inhibit CYP3A metabolism of other HIV PIs; and is being studied to boost HCV PIs
Polypharmacy and the Risk of DDIs with DAAs: Real World Experience

- 75% of patients treated with DAAs at MGUH were taking medications (one or more) that can potentially interfere with CYP3A4 as substrates, inhibitors or inducers
- 9% were on medications that are contraindicated with TVP or BOC and were stopped (statins most commonly)
- Hydroxyzine (for itching) was the most common prescription inhibitor; silymarin the most common OTC inhibitor
- 25% taking CYP3A4 inhibitors had RVR and eRVR vs 63% not taking inhibitors (p=0.001)

*Juneja M et al MGUH (DDW 2013 poster presentation)*

Other considerations prior to Tx

- Use of eltrombopag to boost platelets
- Active substance abuse: alcohol, drugs
- Methadone maintenance
- Co-infection with HIV
- Pre- and post-liver transplant status
- Pre- and post-renal transplant
- Vit D deficiency
- Insulin resistance
CUPIC Trial: a cautionary tale

- 33–45% of 292 cirrhotics receiving PI regimens in France needed hospitalization
- 6 deaths (5 T, 1 B) from infection, decompensation
- Need for epo in 46–54%
- Transfusions in 16% T, 6.3% B
- Grade ¾ toxicities:
  - anemia 11.4% T, 4.4% B
  - thrombocytopenia 12.7% T, 6.3% B
  - Infection 6.5% T, 2.4% B
  - Rash 4.8% T
  - Hepatic decompensation 2% T, 2.9% B

Hezode et al. EASL 2012

Wait or Treat? How to Decide?

- **Treat now**
- GT 1 with F3 or F4, treatment-naïve or prior relapser
- GT 2–6 with F3 or F4, treatment-naïve
- Extrahepatic manifestations (cryoglobulinemia, PCT, GN, B cell lymphoma)
- No contraindications to Tx
- Good motivation, compliance
- Concern about sexual, vertical or household transmission
Treat or Wait?

*Wait for new Tx*
- GT 1 F0–F2 with prior null response
- GT 2 or 3 with prior relapse or non-response
- Absolute or Relative contraindications to Tx
- Actively trying to start a family
- History of non-compliance
- Poorly tolerated Tx in the past or significant concern about side effects

Treat or Wait?

*Undecided:*
- GT 1  F0–F2 treatment-naïve or prior relapsers
- GT 2–6  F0–F2 treatment-naïve
- any F3–F4 with prior null or partial response
- HIV coinfe...
Treat or Wait?

*Murphy’s Law of HCV:*

*patients with the highest priorities for treatment (e.g. advanced fibrosis, rapidly progressive disease)*

*will have the most side effects, treatment-limiting events and the lowest response rates!*