Extrahepatic Complications of Hepatitis C Virus infection

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Recognize the extrahepatic complications of HCV that are of high priority for HCV therapy.
• Manage extrahepatic complications in the era of IFN-free HCV regimens.
Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Extrahepatic disorders associated with HCV infection

Mixed cryoglobulinemia
Membranoproliferative glomerulonephritis
Fatigue
Cognitive impairment
Polyarthritis
Sicca syndrome
Porphyria cutanea tarda
Non-Hodgkin B-cell lymphoma
Insulin resistance &/or Type 2 DM
Myocardial dysfunction
Osteoporosis/Fracture

Adapted from F. Negro. Nature Reviews Gastroenterology and Hepatology 2014
According to the AASLD/IDSA HCV guidelines, patients with the following extrahepatic manifestations should be prioritized for HCV Rx EXCEPT:

a) Insulin Resistance
b) Debilitating Fatigue
c) Cryoglobulinemia with end organ manifestations
d) Porphyria Cutanea Tarda
e) Nephrotic Syndrome
# Highest Priority for HCV Treatment

**Highest Risk for Severe Complications**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rating</th>
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<tbody>
<tr>
<td>Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td>Organ Transplant</td>
<td>Class I, Level B</td>
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<tr>
<td>Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations</td>
<td>Class I, Level B</td>
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<tr>
<td>(eg. vasculitis)</td>
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<tr>
<td>Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis</td>
<td>Class IIa, Level B</td>
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</tbody>
</table>

Class I: evidence &/or general agreement that tx is beneficial, useful, and effective  
Class IIa: weight of evidence &/or opinion is in favor of usefulness and efficacy  
Level A: Data from multiple randomized clinical trials, meta-analyses, or equivalent  
Level B: Data derived from single randomized trial, non-randomized studies, or equivalent  

AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C (April 2015); [www.hcvguidelines.org](http://www.hcvguidelines.org)
### High Priority for HCV Treatment

**High Risk for Severe Complications**

<table>
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<th>Condition</th>
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<tbody>
<tr>
<td>Fibrosis (Metavir F2)</td>
<td>Class I, Level B</td>
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<tr>
<td>HIV-1 coinfection</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV) coinfection</td>
<td>Class IIa, Level C</td>
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<tr>
<td>Other coexistent liver disease (eg. NASH)</td>
<td>Class IIa, Level C</td>
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<tr>
<td><strong>Debilitating fatigue</strong></td>
<td>Class IIa, Level B</td>
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<tr>
<td><strong>Type 2 Diabetes</strong></td>
<td>Class IIa, Level B</td>
</tr>
<tr>
<td><strong>Porphyria cutanea tarda</strong></td>
<td>Class IIb, Level C</td>
</tr>
</tbody>
</table>

Class I: evidence &/or general agreement that tx is beneficial, useful, and effective  
Class IIa: wt of evidence &/or opinion in favor of usefulness and efficacy; Class IIb: Usefulness, efficacy less well established  
Level A: Data from multiple randomized clinical trials, meta-analyses, or equivalent  
Level B: Data derived from single randomized trial, non-randomized studies, or equivalent  
Level C: Consensus opinion of experts, case studies, and standard of care

58 yo HCV GT 1a, mod fibrosis with fatigue, lower extremity rash, and rapid Cr rise to 2.89. Now what?

a) Check cryoglobulin levels
b) Consult Liver, Derm, and Renal
c) Start sofosbuvir/ledipasvir
d) All of the above
e) a and b only
What is cryoglobulinemia?

- Presence of immunoglobulins (Ig) in serum that precipitate when below nl body temperature (4°C).
- **Type 1** (isolated monoclonal IgM); commonly associated with lymphoproliferative disorders
- **Type 2** (monoclonal IgM and polyclonal IgG) and **Type 3** (polyclonal IgM) with mixed immune complexes; common in pts with chronic viral infections (HCV, HBV, CMV) and lupus, RA.

Cacoub P et al Digestive and Liver Disease 2014; Lauletta G. Practical Management of Chronic Viral Hepatitis 2013
Cryoglobulinemia in HCV

- In pts with mixed cryoglobulinemia, 50 – 100% have HCV infection.
- In pts with HCV, 10 – 50% have evidence of cryoglobulins on lab testing.
- Most with cryoglobulinemia have no or non-specific symptoms.

Cacoub P et al Digestive and Liver Disease 2014
Cryoglobulinemia clinical syndromes reported in HCV

- Fatigue, Arthralgia, Myalgia (35 – 54%)
- Renal disease [e.g. membranoproliferative glomerulonephritis (GN)] (27 – 30%)
- Palpable purpura (18 – 33%)
- Neurologic disease (e.g. peripheral neuropathy, central nervous system vasculitis) (11 – 30%)
- Sicca syndromes (10 – 25%)

Cacoub P et al Digestive and Liver Disease 2014
Cryoglobulinemic vasculitis

- Immune complexes (IC) in wall of small vessels activates complement cascade.
- Dx: h/o HCV, palpable purpura (occurs in ~90%), low complement (C3, C4) levels, circulating cryoglobulins, skin bx with small vessel inflammation.
Tx of cryoglobulinemia vasculitis

• Little published data available on IFN-free regimens; high SVR rates, low risk of side effects support their use.
• For organ threatening and/or rapidly progressive disease (severe neuropathy, renal failure, digital ischemia), also treat urgently with:
  – Corticosteroids, cytotoxic agents, plasmapheresis to clear IC
  – Rituximab, a monoclonal antibody that targets B cells (which are responsible for cryoglobulin production)
    • PEG-RBV + rituximab (vs. PEG-RBV) with faster clinical remission, better renal response, higher rates of cryoglobulin clearance

• Consult expert experienced with using these agents

Kidney Injury

- 3 potential mechanisms: (1) Direct viral tissue damage; (2) Insulin resistance; (3) **Systemic immune response (mediated by cryoglobulins)**
- Most common is membranoproliferative GN
- Proteinuria, microscopic hematuria, mild-mod renal insufficiency, low serum C3, C4; renal bx to confirm
- IFN-based regimens shown to reverse proteinuria and nephrotic syndrome, but azotemia can persist.
- No clinical trial data yet available using IFN-free regimens, but high rates of SVR support their use.

AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C (April 2015); www.hcvguidelines.org; www.hepatitisc.uw.edu
Porphyria cutanea tarda

- Caused by reduction of hepatic uroporphyrinogen decarboxylase activity
- ~50% have HCV, especially cirrhosis
- Characterized by photosensitivity, skin fragility, bruising, and vesicles/bullae that can become hemorrhagic
- Tx: iron reduction by phlebotomy to mildly iron-reduced state without anemia.

Insufficient data re: HCV DAAs and SVR, but improvement reported with IFN-based HCV treatment.

AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C (April 2015); www.hcvguidelines.org
~50% of HCV pts have fatigue; may be more common and severe in women and in those with cirrhosis

Sarkar S et al. J Hepatology 2012
Quality of Life in HCV pts with SVR12

Younossi ZM et al J of Hepatology 2014
HCV is associated with IR and DM

Guo et al Scientific Reports 2013

X Guo et al Scientific Reports 2013

ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals
HCV and IR/DM: Mechanisms

Patel JH et al QJM 2010
HCV treatment with PEG-RBV associated with decreases in insulin resistance

Conjeevaram, HS et al. Gastroenterology 2011; 140:469-477
In DM adults, HCV Rx associated with decreased ESRD risk. Untreated HCV+ have greater ESRD risk than HCV-. HCV likely has direct effects on renal disease independent of DM.

Hsu Y et al Hepatology 2014
In DM adults, HCV Rx associated with decreased cardiac events. Untreated HCV+ had similar cardiac risk as HCV-.
HCV effect may be partly mediated through its effect on diabetes. Similar effects for stroke events.

Hsu Y et al Hepatology 2014
Higher incidence of fractures in HIV/HCV-patients vs HIV in Danish cohort

Fig. 1. Cumulative incidence of low-energy fractures (left) and high-energy fractures (right) in HIV-monoinfected patients, HIV/HCV-coinfected patients and population controls.

BMD lower with higher histologic stages of liver fibrosis in patients with viral hepatitis

Schiefke, et al. World J Gastroenterol 2005
CONCLUSION

• HCV is associated with a broad range of outcomes outside of the liver.

• Patients with organ threatening and/or rapidly progressive cryoglobulinemia syndromes should be of highest priority for HCV treatment in consultation with experts (Liver, Renal, Derm).

• HCV treatment may improve long term events such as vascular disease (CVD, stroke) especially in patients with DM, and fracture risk.

• DAAs are expected to have similar results.
Thank you!