Hepatitis C Virus: RNA, Single strand +ve, enveloped

**Classification**
- **Kingdom:** Orthornavirae
- **Phylum:** Kribonviricota
- **Class:** Flaviviricetes
- **Order:** Trematodovirales
- **Family:** Flaviviridae
- **Genus:** Hepacivirus
- **Species:** Hepacivirus C

**Structure**
Small (55-65 nm), spherical, core of RNA surrounded by icosahedral protein capsid, and a host-derived lipid envelope with embedded viral envelope glycoproteins, E1 and E2.

**Genome and function**
- 9.6 kilobases. Single open reading frame, encoding a 3000 AA polyprotein.

**Life Cycle**
1. Entry into host cells occur through complex interactions between viral glycoproteins and cell-surface molecules including CD81, LDL receptor, SCR, DC-SIGN, Claudin-1, and Occludin.
2. +RNA binds to ribosomes via IRES, leading to translation of a 3000 AA polyprotein
3. Polyprotein is cleaved by viral and host proteases into 10 proteins
4. +RNA is copied to −RNA by NS5b (viral RNA polymerase), which then is a template for NS5b to replicate more strands of +RNA. Replication is on intracellular lipid membranes.
5. Components cluster into a “membranous web” (NS4B expression dependent) in the cytoplasm and are assembled into new virions, and then exported. Release may involve VLDL secretory pathway. [HCV envelope similar to VLDL and LDL and HCV associates with apolipoproteins – may lead to covering of E1 and E2 GP.]

Replicates within hepatocytes (and possibly PBMCs), ~10^{12} virions per day.

**Genetic Diversity**
The viral RNA polymerase very error-prone—many mutations each day. All the extant genotypes appear to have evolved from G/T 1 subtype 1b.

7 known genotypes and > 80 subtypes-
HCV genetic diversity (left) far exceeds HIV (right).

Genotyping by sequencing or line-probe hybridization of 5’UTR.

**History**
1970s – NANB hepatitis recognized as commonest cause of transfusion-related hepatitis. Transmissible in chimpanzees, but agent unknown.
1989—HCV named and genome cloned.
1990s - Replicon system developed (subgenomic RNAs inserted into Huh7 cell lines and copied)
2005 – complete cell culture system for propagating HCV described.
Pathogenesis
Viral persistence in 70-85% of those infected despite antibody and cellular immune response against all viral antigens. Unclear why. Viral genetic variation contributes. Host response (macrophage derived TNF-alpha) causes hepatocyte injury. Host genetics- IL-28B CC more likely to clear spontaneously (55%) vs TT (10-15%). % with CC genotype varies by ancestry- 23-55% African, vs 90-100% East Asian.

Natural history / clinical
Most new infections are asymptomatic. Acute symptomatic hepatitis in 30-40%, jaundice in 25%. Viral RNA detectable in serum within 4 days-6 weeks of exposure (>95% within 1 week following contaminated blood transfusion). ALT elevation usually 6-12 weeks post exposure, and lasts up to 12 weeks.

Acute infection progresses to chronic disease in about 75%, - risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). 20%-30% of people with chronic HCV develop cirrhosis, generally at 20–30 yrs. Higher with co-factors (e.g. ETOH, HIV, HBV). HCC develops in 3% / year once cirrhosis established. Long term natural history varies: female gender lower risk (possible due to less co-factors) and also more likely to spontaneously recover (e.g. 2% cirrhosis at 17 years in 50,000 Irish women infected following anti-D vs 30% cirrhosis after 11-years follow up in US IDUs). Other conditions:
- mixed cryoglobulinemia (usually type II form)
- autoimmune disorders, pos RF (20-30%)
- B-cell lymphoproliferative disorders.
- pancreatic carcinoma risk
- occult infection – virus detected with ultrasensitive testing ? relevance

Epidemiology
Circa 170 million infected worldwide (2019). Oz: 182,144 at end of 2017. 2019:

1990s blood transfusion (blood screening 1992 USA), needle stick injury: [HNE down by one third in 2020 (needless device adoption); no known HCV acquisitions:

<table>
<thead>
<tr>
<th>Year / Month</th>
<th>Number of Exposure Incidents</th>
<th>Number of Needlestick Incidents</th>
</tr>
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<tbody>
<tr>
<td>2020-01</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>2020-02</td>
<td>5</td>
<td>19</td>
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<td>2020-03</td>
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<td>14</td>
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<td>2020-04</td>
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<td>11</td>
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<tr>
<td>2020-05</td>
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<td>23</td>
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<tr>
<td>2020-06</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>87</td>
</tr>
</tbody>
</table>

Who to test (ASHM)
Box 2 Populations to consider for a hepatitis C virus (HCV) screening test
- People who inject drugs or who have ever injected drugs
- People in custodial settings
- People with tattoos or body piercing
- People who received a blood transfusion or organ transplant before 1990
- People with coagulation disorders who received blood products or plasma-derived clotting factor treatment products before 1993
- Children born to HCV-infected mothers
- People infected with human immunodeficiency virus (HIV) or hepatitis B virus
- Sexual partners of an HCV-infected person (individuals at higher risk of sexual transmission include men who have sex with men and people with HIV-HCV co-infection)
- People with evidence of liver disease (persistently elevated alanine aminotransferase level)
- People who have had a needle-stick injury
- Migrants from high-prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Asia)

Annual HCV serology recommended for seronegative pts with ongoing risk factors. Annual HCV PCR (Medicare ok) for treated or pcr negative seropos pts with ongoing risk factors.

Pre-treatment assessment
- Confirm diagnosis HCV infection (PCR)
- Identify genotype of HCV (optional 2020)
- Document HCV treatment history
- Evaluate for presence of cirrhosis: Fibroscan or APRI score - AST/PLT ratio (In a meta-analysis of 40 studies, investigators concluded that an APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis)
- Look for HBV/HIV coinfection
- Evaluate for coexisting liver diseases
- Consider concomitant medications and recreational substances.
- Evaluate renal function
- Discuss the need for contraception
- Discuss importance of treatment adherence.

Alcohol avoidance, vaccinate against hepatitis A and B. Avoid NSAIDS in cirrhosis.
Treatment
Virtually all suitable for Direct acting antiviral (DAA) therapy, including those previously intolerant of or ineligible for IFN therapy. Three classes:

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>NS5B Polymerase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>Deacitavir</td>
<td>Daclizuvir</td>
</tr>
<tr>
<td>Gileadrevir</td>
<td>Elnavir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Orazprevir</td>
<td>Ledipasvir</td>
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<tr>
<td>Paritaprevir</td>
<td>Omibatvir</td>
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<tr>
<td>Simeprevir</td>
<td>Pibrentasvir</td>
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<tr>
<td>Telaprevir</td>
<td>Velpatasvir</td>
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<td>Voxilaprevir</td>
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Goal of treatment is cure, or SVR, defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased. SVR is associated with improvement in quality of life, loss of infectivity, regression of liver fibrosis and cirrhosis, reduction in the risk of liver failure and reduction in the risk of liver-related and all-cause mortality.

Pan-genotypic treatment protocols

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>RB burden</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cirrhosis</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>12 weeks</td>
<td></td>
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</tbody>
</table>

HCV genotype 3 was previously the most difficult HCV genotype to treat - see these detailed recs. However pan G/T rx above has > 90% cure rate. Highest cure with triple regimen.

Resistance testing (ICPMR)

Resistance-associated substitutions (RAS) can occur with all approved DAs. RAS testing not recommended for treatment-naive people. Consider NS3, NS5B and NS5A RAS by direct sequencing if failure of DAA treatment.

Hepatocellular carcinoma surveillance

Unclear whether DAA therapy influences HCC recurrence in people with cirrhosis based on published data. ASHM recs: U/S within 1 mth before DAA therapy for all with cirrhosis and thence 6 -mthly (sensitivity of u/s alone for detecting HCC at any stage 78% (95% CI 67-86 percent) and for early-stage HCC is 45% (CI, 30-62 percent) (UptoDate)).

No data to suggest that HCC risk may be increased in people with no cirrhosis- screening not recommended.

HealthPathways referral criteria (HNE)

- Arrange emergency department admission if vomiting, encephalopathy, raised INR, or ALT greater than 1000 units/L.
- Arrange urgent referral to Viral Hepatitis Service or private gastroenterologist if new liver lesion or indications of worsening hepatic decompensation are evident.
- Arrange routine referral to Viral Hepatitis Service or private gastroenterologist if:
  - co-infection with HIV or HBV.
  - suspected or confirmed cirrhosis.
  - concerns for treatment adherence.
  - prior anti-HCV treatment experience.
  - chronic kidney disease (CKD) stage 4 or 5.
  - pregnancy and breastfeeding.
  - individual requests specialist input.
  - complications of liver disease, co-morbidities, or additional liver disease supported.
  - SVR not achieved.

Public health and prevention

HCV can remain viable outside the host for 2 days at 37°C and 6 weeks at 4°C.

Safe supply and harm minimization (needle and syringe programs). Healthcare – needleless devices.

DAAs: increasing treatment in IDU population modelled to have dramatic effect on reducing HCV prevalence. Australian on track to ‘elimination’ by 2030. Australia – capped cost of DAAs arranged.

No licensed vaccine – significant challenges and priority becoming less with DAA availability.

References

- Viral Hepatitis and HIV prescribing summary – Davis 2020
- ASHM HCV Guidelines
- Hepatitis Australia
- Wikipedia
- UptoDate
- University of Washington HCV resource
- Bailey et al 2019: Approaches, Progress, and Challenges to Hepatitis C Vaccine Development