The A, B, C, D, & E of Viral Hepatitis

A Case Based Update of Viral Hepatitis
Viral Hepatitis - Historical Perspectives

- "Infectious" (A)
- "Serum" (B, D)
- Enterically transmitted (E)
- Parenterally transmitted (C)
- F, G, TTV, ? other

Viral hepatitis
# Type of Hepatitis

<table>
<thead>
<tr>
<th>Type of Hepatitis</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of virus</td>
<td>feces</td>
<td>blood/blood-derived body fluids</td>
<td>blood/blood-derived body fluids</td>
<td>blood/blood-derived body fluids</td>
<td>feces</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>fecal-oral</td>
<td>percutaneous permucosal</td>
<td>percutaneous permucosal</td>
<td>percutaneous permucosal</td>
<td>fecal-oral</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Prevention</td>
<td>pre/post-exposure immunization</td>
<td>pre/post-exposure immunization</td>
<td>blood donor screening; risk behavior modification</td>
<td>pre/post-exposure immunization; risk behavior modification</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>
Hepatitis A - Clinical Features

- Incubation period: Average 30 days
  Range 15-50 days

- Jaundice by age group:
  <6 yrs, <10%
  6-14 yrs, 40%-50%
  >14 yrs, 70%-80%

- Complications: Fulminant hepatitis
  Cholestatic hepatitis
  Relapsing hepatitis

- Chronic sequelae: None
40 yo NP visited her sister in D.C.
- Fatigue and flu like symptoms minus URI sxs 20 days later
- Presented to PCP day 28
- Sent to ED due to elevated LFTs
- Loss of appetite and early satiety
- RUQ pain
- Elevated LFTs = AST 202, ALT 300, Total Bili 5.3
- Developed jaundice on day 32
Hepatitis A Infection
Typical Serological Course

Months after exposure

0 1 2 3 4 5 6 12 24

Fecal HAV
Symptoms
ALT
Total anti-HAV (IgG)
IgM anti-HAV

Titre
Hepatitis A Virus Transmission

- Close personal contact
  (e.g., household contact, sex contact, child day care centers)

- Contaminated food, water
  (e.g., infected food handlers, raw shellfish)

- Blood exposure (rare)
  (e.g., injecting drug use, transfusion)
Hepatitis A Vaccination Strategies

Epidemiologic Considerations

- Many cases occur in community-wide outbreaks
  - no risk factor identified for most cases
  - highest attack rates in 5-14 year olds
  - children serve as reservoir of infection
- Persons at increased risk of infection
  - travelers
  - homosexual men
  - injecting drug users
Hepatitis A Prevention - Immune Globulin

- Pre-exposure
  - travelers to intermediate and high HAV-endemic regions

- Post-exposure (within 14 days)
  - Routine
    - household and other intimate contacts
  - Selected situations
    - institutions (e.g., day care centers)
    - common source exposure (e.g., food prepared by infected food handler)
Case Example – Hepatitis A

- 40 yo NP visited her sister in D.C.
- Fatigue and flu like symptoms minus URI sx 20 days later
- Presented to PCP day 28
- Sent to ED due to elevated LFTs, Loss of appetite and early satiety RUQ pain
- Elevated LFTs = AST 202, ALT 300, Total Bili 5.3
- Discharged home
- Returned to work 8 weeks later when jaundice resolved, then had some relapse of symptoms, full resolution week 16
Hep B Case

- 35 yo Vietnamese Female, newly pregnant at 13 weeks, routine screening shows her Hep B positive – Surface Ag positive
- E antigen positive, DNA 70 million, AST 22, ALT 18, ALK Phos 40, Bili 0.8
- Mother and 2 brothers with Hep B
- Daughter has been vaccinated, Spouse unknown vaccine or disease status
- Follow-up at 28 weeks shows DNA of 54 million
Hep B Case #2

- 71 yo Chinese female, per records Hep B “carrier”
- Noted to have early satiety, jaundice, RUQ abdominal pain and extreme fatigue for several weeks
- Family brings her to urgent care as she is losing weight, having nausea and feeling worse
- Noted to have scleral icterus and jaundice, hepatosplenomegaly on exam 3 cm below the costal margin
- From previous PCP notes 10 lb weight loss on exam today
- Potassium of 3.0, Sodium 132, AST 1125, ALT 1425, Total Bili 14.2, Alk Phos 220, BUN 1.5, Creat 37, AFP 1218
- She is sent to the ER from Urgent Care and admitted
Hepatitis B - Clinical Features

- Incubation period: Average 60-90 days
  Range 45-180 days

- Clinical illness (jaundice):
  <5 yrs, <10%
  5 yrs, 30%-50%

- Acute case-fatality rate: 0.5%-1%

- Chronic infection:
  <5 yrs, 30%-90%
  5 yrs, 2%-10%

- Premature mortality from chronic liver disease: 15%-25%
Serologic tests for HBV

HBsAg (surface antigen)  HB virus present
HBeAg (“e” antigen)  HBV replicating/”pre-core mutants”
HBcAb (“core” antibody)  Ever infected/ acute or chronic
HBsAb (surface antibody)  Infx over/immune
HBV DNA level  Quantifies virus
Hepatitis B Labs

**Acute**

- HBV Surface Antigen (HBsAg) – Surface protein on the Hep B virus; it can be detected in high levels in serum during acute or chronic hepatitis B viral infection
- Total HBV core antibody (anti-HBc) – appears at the onset of symptoms in acute Hep B and persists for life
- IgM antibody to Hep B core antigen (IgM anti-HBc) – positivity indicates recent infection with hepatitis B virus (<= 6 months), indicates acute infection
- HBV E-Antigen (HBeAg) – is found in the early phase of hepatitis B infection soon after surface antigen becomes detectable, both antigens rise during periods of viral replication, and correlates with infectivity.
- HBV DNA – marker of active HBV replication, DNA levels are detectable by 30 days following infection, DNA can be detected approximately 21 days before HBsAg typically appears in the serum

**Chronic**

- HBV Surface Antigen (HBsAg) – Surface protein on the Hep B virus; it can be detected in high levels in serum during acute or chronic hepatitis B viral infection
- Total HBV core antibody (anti-HBc) – appears at the onset of symptoms in acute Hep B and persists for life
- HBV E-Antigen (HBeAg) – indicates presence of active HBV replication and high infectivity, in the life cycle of the virus the conversion of E-antigen positive to E-antigen negativity can lead to either resolution of the infection or chronic hepatitis
- HBV E-antibody (HBeAb) – can indicate inactivity of the virus and low infectivity but in the presence of detectable viral DNA levels indicates active viral replication
- HBV DNA – marker of active HBV replication, DNA + HBeAg or HBeAb help characterize the state of the patients infection
Acute Hepatitis B Virus Infection with Recovery  Typical Serologic Course

Weeks after Exposure

- **Symptoms**
  - HBeAg
  - anti-HBe

- **Titre**
  - HBV DNA
  - Total anti-HBc

- **HBsAg**
- **IgM anti-HBc**
- **anti-HBs**

0 4 8 12 16 20 24 28 32 36 52 100
Figure 1 Natural course of chronic HBV infection

Permission obtained from Elsevier Ltd © Lok, A. S.

Kwon, H. & Lok, A. S. (2011) Hepatitis B therapy
Outcome of Hepatitis B Virus Infection by Age at Infection

Chronic Infection (%)

Symptomatic Infection

Age at Infection

- Birth
- 1-6 months
- 7-12 months
- 1-4 years
- Older Children and Adults
## Concentration of Hepatitis B Virus in Various Body Fluids

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low/Not Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
<td>semen</td>
<td>urine</td>
</tr>
<tr>
<td>serum</td>
<td>vaginal fluid</td>
<td>feces</td>
</tr>
<tr>
<td>wound exudates</td>
<td>saliva</td>
<td>sweat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>breastmilk</td>
</tr>
</tbody>
</table>
Hepatitis B Virus
Modes of Transmission

- **Sexual** - sex workers and homosexuals are particular at risk.

- **Parenteral** - IVDA, Health Workers are at increased risk.

- **Perinatal** - Mothers who are HBeAg positive are much more likely to transmit to their offspring than those who are not. Perinatal transmission is the main means of transmission in high prevalence populations.
Chronic Hepatitis B

- HBV DNA and ALT ↑
  - Treatment

- HBV DNA ↑ and ALT normal
  - Consider liver biopsy

- HBV DNA and ALT ↓
  - No Treatment

  - Moderate/Severe histologic disease
    - Treatment

  - No or mild histologic disease
    - No Treatment
VEMLIDY is a novel, targeted prodrug of tenofovir for the treatment of chronic hepatitis B in adults with compensated liver disease.

Due to enhanced plasma stability, VEMLIDY demonstrates more efficient delivery of tenofovir to hepatocytes vs VIREAD. **A 25-mg oral dose of tenofovir alafenamide (TAF) in VEMLIDY resulted in 89% lower plasma concentrations of tenofovir vs a 300-mg oral dose of VIREAD, thereby reducing systemic exposure.**

**INDICATION**
VEMLIDY is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease.

**IMPORTANT SAFETY INFORMATION**
BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs.
- Discontinuation of anti-hepatitis B therapy, including VEMLIDY, may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VEMLIDY. If
Hepatitis B treatments

- Entecavir 0.5 mg and 1.0 mg daily – No renal issues, no problems with Phosphorous levels

- Tenofovir Disoproxil 300 mg – low rates of resistance, potential for renal issues and bone loss, can cause hypophosphatemia

- Tenofovir Alafenamide 25 mg – Pro-drug of Tenofovir, not associated with renal or bone loss issues, no issues with phosphorous

- Pegylated Interferon – only potentially curative treatment, but risks or therapy outweigh the benefits
HBV DNA undetectable- 1yr

Bar chart showing the percentage of undetectable HBV DNA after 1 year of treatment with different drugs:

- LAM
- ADV
- ETV
- LdT
- TDF
- PEG

Colors:
- HBeAg +
- HBeAg -
HBsAg clearance-1yr

%  
100  
80  
60  
40  
20  
0  
LAM  ADV  ETV  LdT  TDF  PEG  
HBeAg +  HBeAg -
Hepatitis B

Elevated serum ALT
Males >30 IU/L; females >19 IU/L

Screening ‘at-risk’ patient

HBsAg pos

If not previously drawn:
- Anti- HAV (total)
- Anti- HCV
- HBeAg/ HBeAb

Vaccinate against hepatitis A

If HBsAg pos:

HBV DNA (quant)

- Treatment not initiated
  - Repeat HBV DNA q6mo
- Treatment initiated
  - Repeat HBV DNA q4mo

Consideration of therapy and/or biopsy¹

Treatment completed²

See hepatitis C algorithm

Refer to hepatology

Begin age-appropriate hepatoma screening
Hepatoma Screening

- We utilize RUQ ultrasound and AFP tumor markers for hepatoma screening – this is a AASLD guidelines or will be when next is released to put AFP back into the recommendations

- Know your local resources – tumor boards at Portland Providence Medical Center, Legacy and OHSU if you have concerns or questions about something you find on imaging

- Definitive testing for Hepatoma is a Triple Phase CT or MRI, also called a dynamic liver exam
Hepatitis D - you can’t have D if you don’t have B!

- The virus represented by Hepatitis D needs the presence of Hepatitis B to survive in the human body.
- When you check for Hepatitis B you should check for D.
- Makes it less likely for Hep B to become a chronic infection, but can occur.
Hep B Case #1

- 35 yo Vietnamese Female, newly pregnant at 13 weeks, routine screening shows her Hep B positive - Surface Ag positive
- E antigen positive, DNA 70 million, AST 22, ALT 18, ALK Phos 40, Bili 0.8
- Mother and 2 brothers with Hep B
- Daughter has been vaccinated, Spouse unknown vaccine or disease status
- Follow-up at 28 weeks shows DNA of 54 million
- Treat for last trimester with Tenofovir - safe in 3rd trimester
- Stop treatment at birth
- Check labs through first 6 months after birth - if her chems stay normal no need for treatment, if they do not improve restart treatment and stop breastfeeding
- She did not require further treatment - continuing labs every 6 months with her PCP
Hep B Case #2

- 71 yo Chinese female, per records Hep B “carrier”
- Noted to have early satiety, jaundice, RUQ abdominal pain and extreme fatigue for several weeks
- Family brings her to urgent care as she is losing weight, having nausea and feeling worse
- Noted to have scleral icterus and jaundice, hepatosplenomegaly on exam 3 cm below the costal margin
- From previous PCP notes 10 lb weight loss on exam today
- Potassium of 3.0, Sodium 132, AST 1125, ALT 1425, Total Bili 14.2, Alk Phos 220, BUN 1.5, Creat 37, AFP 1218
Hep B Case #2

- Started on Tenofovir 300 mg
- Supported with IVF and nutrition in the inpatient setting – high protein low sodium diet
- CT Dynamic Liver showed two <2 cm hyperenhancing lesions with “washout” diagnostic for Hepatocellular Carcinoma
- Treated with Y90 and XRT
- Still a patient 2 years later
The prevalence of chronic liver disease is ~15%

1.4 million  30% aware

5.2 million  75% unaware

In Oregon…

Prevalence of HCV 2-3%
90,000 Hep C patients
Hep C Case #1

- 24 year old mixed race female
- Used heroin and meth from age 16 to 23
- Clean and sober for 5 months
- Tested positive for Hep C ab in rehab
- Presents to clinic with her mother for discussion of treatment
- Recent flu like illness and massive fatigue that are now gone
- No recent LFTs, never had a HCV Quant PCR
Hep C Case #2

- 55 yo African American male
- Uses heroin intranasal now but prior IV use
- Hep C for at least 29 years
- Hx of Hep B and jaundice but told that he cleared it
- Prior Interferon/Ribavirin non-responder
- Told at that time he was cirrhotic
- Has not seen primary care in 10 years, recently re-established and now wants “Harvoni,” like on TV per referral
- Has RUQ pain, changes in appetite and weight loss
Hep C Case #3

- 78 yo Caucasian female with a hx of type 2 diabetes, hyperlipidemia atrial fibrillation, fatty liver disease and CAD diagnosed on routine screening 2 months ago through PCP – elevation in LFTs always blamed on Fatty Liver
- Only possible exposure was blood transfusion due to a duodenal ulcer in 1983
- Scared about her grandchildren and kids getting Hep C
- Worried about telling her husband of 49 years – could he have given this to her?
- Son used IV drugs – maybe he gave this to her – no needle contact
- Feels “Normal, at least as normal as you can be at my age and my ticker!”
Hepatitis C Virus Infection

Typical Serologic Course

<table>
<thead>
<tr>
<th>Titre</th>
<th>Months</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-HCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time after Exposure

0 1 2 3 4 5 6 1 2 3 4
The Changing Face of HCV in the US

Who to screen

- **Baby Boomers** – persons born between 1945 and 1965

- **High-risk behaviors**
  - Injection-drug use
  - Intranasal illicit drug use

- **High-risk exposures**
  - Long-term hemodialysis (ever)
  - Tattoo in an unregulated setting
  - History of needle sticks, sharps, or mucosal exposures to HCV-infected blood
  - Children born to HCV-infected women
  - Prior recipients of transfusions or organ transplants prior to July, 1992
  - Persons who were ever incarcerated
  - Other Medical Conditions associated with high risk
    - HIV infection
    - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
Hep C Case #1

- 24 year old bi-racial female
- Used heroin and meth from age 16 to 23
- Clean and sober for 5 months
- Tested positive for Hep C ab in rehab
- Presents to clinic with her mother for discussion of treatment
- Recent flu like illness and massive fatigue that are now gone
- No recent LFTs, never had a HCV Quant PCR
Hep C Case #1

- AST 22, ALT 20, T Bili 0.7, Alk Phos 65
- HCV Quant <15
- Hep B S Ag non-reactive
- Hep B S Ab <3.10
- Hep B Core total Ab non-reactive
- HIV non-reactive
Spontaneous Viral Clearance

- Between 25-30 % of patients will spontaneously clear Hepatitis C
- Usually a younger co-hort
- We often see this in young recently clean patients
- Often have a robust immune response with “flu-like” prodrome and very elevated transaminases that then fall to normal along with a negative viral quantitative PCR
How to screen

Recommended Testing Sequence for Identifying Current HCV Infection

HCV Antibody

Nonreactive

No HCV antibody detected

STOP*

Reactive

Not Detected

HCV RNA

No current HCV infection

Additional testing as appropriate†

Detected

Current HCV infection

Link to care

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
REPORT

A NATIONAL STRATEGY FOR THE ELIMINATION OF HEPATITIS B AND C

PHASE TWO REPORT
Baby boomers (+ other high-risk populations)

Screen for HCV
- Positive:
  - Vaccinations

Assess for Fibrosis
- FibroMeter/Scan / +/- biopsy
- F0-2

Compensated F3-4, F2+ manifestations

Surveillance
- FibroSure/Scan

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of every 6 months evaluation - AASLD/IDSA Guidance

Hep panel, CBC, PT/INR
- HCV quantitative PCR
- HCV genotype
- Anti-HAV; HBsAg/Ab
- Fe/TIBC/ferritin

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. (Boursier, 2012) A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making - AASLD/IDSA Guidance

Role of PCP
- Ongoing cirrhosis care
- Patient education
- Prescribes drug
- Side effect management
- Dose adjustment
- Monitors compliance

340b pharmacy
- Dispenses drug

GI or Hepatology
- Ongoing cirrhosis care
Expected results of cohort screening

- 1,000 adult patients
  - Efficiently identify birth cohort 1945-1965
    - Electronic prompt

- 330 baby boomers
  - ~1/3 of adults are in 1945-1965 cohort

- 10 HCV antibody positive
  - 1 of 30 baby boomers
    - 1 of 23 men baby boomers
    - 1 of 12 African American men baby boomers

- 7 HCV RNA positive
  - 15-30% of HCV antibody patients will spontaneously clear

- 3 with more advanced fibrosis
- 4 with mild fibrosis

- Up to 25% of baby boomers may have cirrhosis
  - 75% of cirrhotic patients are men

Davis, Gastro 2010;138:513
Baby boomers (+ other high risk pops)

Screen for HCV positive

Assess for Fibrosis
FibroMeter/Scan-Elastography / +/-biopsy

Surveillance
FibroSure/Scan

EPIC workbench - no PCP alert
Hep panel, CBC, PT/INR
HCV quantitative PCR
HCV genotype
Anti-HAV; HBsAg/Ab
Fe/TIBC/ferritin

This will be you soon!
Compensated F3-4, F2+manifestations

Role of PCP
Ongoing cirrhosis care

340b pharmacy
Dispenses drug

PCPs / ID / NPs
Patient education
Prescribes drug
Side effect management
Dose adjustment
Monitors compliance

GI or Hepatology

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of every 6 months evaluation - AASLD/IDSA Guidance

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. (Boursier, 2012) A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making - AASLD/IDSA Guidance

Baby Boomers – persons born between 1945 and 1965
High-risk behaviors
- Injection-drug use
- Intranasal illicit drug use

High-risk exposures
- Long-term hemodialysis (ever)
- Tattoos in an unregulated setting
- History of needlesticks, sharps, or mucosal exposures to HCV-infected blood
- Children born to HCV-infected women
- Prior recipient of transfusions or organ transplants prior to July 1992
- Exposure to percutaneous injury
- Other medical conditions associated with HCV infection
- Chlamydia, syphilis
- Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
Non-Invasive Markers

- Physical assessment (Liver stiffness measurement)
  - US transient elastography (Fibroscan® or)
  - MR elastography
  - US acoustic radiation force impulse (ARFI) elastography

- Chemical assessment (blood test)
  - Direct markers of fibrogenesis (proprietary)
    - Fibrotest (Fibrosure®)
    - ELF (European liver fibrosis) panel
  - Indirect markers of fibrosis (routine lab)
    - APRI score
    - Fib-4
    - Fibrometer

Currently in use

Potential alternatives

- Physical measures tend to outperform chemical assessment
  - MR > US (Fibroscan) ~ ARFI > Direct > Indirect
  - Combination?
Hepatitis C patient

Simultaneously draw:
Fasting hep panel, CBC, PT/INR, and FibroMeter

Order total abd u/s + elastography

Comparison of:

- APRI, FIB-4 scores
- Liver appearance
- Spleen size
- Portal vein diameter
- Presence or absence of ascites

APRI
- <0.5 minimal fibrosis
- >0.5-1.5 progressive fibrosis
- >1.5 Likely cirrhotic

FIB-4
- <1.45 advanced fibrosis unlikely
- >3.25 likely advanced fibrosis

As both require a fasting state will do both when the patient undergoes SWE exam.
**APRI** = \( \frac{\text{AST Level (IU/L)}}{\text{AST (Upper Limit of Normal) (IU/L)}} \times \frac{\text{Platelet Count (}10^9/L)}{\text{x 100}} = \)

**Fibrosis-4 (FIB-4) Calculator**

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (}10^9/L)} \times \sqrt{\frac{\text{ALT (U/L)}}{}}
\]

**APRI**
- **<0.5** minimal fibrosis
- **>0.5-1.5** progressive fibrosis
- **>1.5** Likely cirrhotic

**FIB-4**
- **<1.45** advanced fibrosis unlikely
- **>3.25** likely advanced fibrosis
Liver Fibrosis, Chronic Viral Hepatitis (Echosens FibroMeter)

Patient Score (Range 0-1)
FibroMeter (fibrosis score) 0.24  F1 [F1-F2]
Predominance of F1, but F2 is possible
CirrhoMeter (cirrhosis score) 0.01  F1 [F1-F2]
Predominance of F1, but F2 is possible
InflaMeter (activity score) 0.35  A1/A2
Equal probability between A1 and A2

Patient Blood Marker Results

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result</th>
<th>Reference Interval</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-2-Macroglobulin</td>
<td>261</td>
<td>131-283</td>
<td>mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>21</td>
<td>9-40</td>
<td>IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>11</td>
<td>5-40</td>
<td>IU/L</td>
</tr>
<tr>
<td>GGT</td>
<td>9</td>
<td>7-33</td>
<td>IU/L</td>
</tr>
<tr>
<td>BUN</td>
<td>14</td>
<td>7-20</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>171</td>
<td></td>
<td>u/L</td>
</tr>
<tr>
<td>Prothrombin Index*</td>
<td>96</td>
<td>90-120</td>
<td>%</td>
</tr>
</tbody>
</table>

Interpretive Information
- Calculations for the final report are based on accurate data for age, gender, and platelet count. If any of this information needs to be corrected, please contact ARUP Client Services to request a recalculations. Client Services may be contacted at (800) 242-2787.
- The Echosens FibroMeter profile serves as a surrogate marker of liver fibrosis, cirrhosis, and necro-inflammatory activity. A propriety algorithm calculates and compares results from 7 blood markers along with age and gender to provide a patient score (from 0 to 1) and a correlated fibrosis stage (Metavir F0-F4) and activity grade (Metavir A0-A3). The fibrosis/cirrhosis score is further evaluated by a rules-based system to detect anomalous profile results which may modify the fibrosis/cirrhosis score as needed.
- Results should be interpreted in conjunction with the patient's clinical history; particularly when the rules-based system has modified the scores.

*Metavir is a histological scoring system for determining the extent of liver fibrosis and inflammation.
1. STAGE OF FIBROSIS (F scale)
- F0 = no fibrosis
- F1 = portal fibrosis without septa
- F2 = portal fibrosis with few septa
- F3 = numerous septa without cirrhosis
- F4 = cirrhosis

2. GRADE OF NECRO-INFLAMMATORY ACTIVITY (A scale)
- A0 = no activity
- A1 = mild activity
- A2 = moderate activity
- A3 = severe activity

* Patient result provided by client.
3. The Prothrombin Index test expresses the Prothrombin Time (PT) as a percentage of normal, and is used to standardize PT results across different instrument/reagent combinations. Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement B: aruplab.com/CS

END OF CHART
Liver biopsy >$2,000
• Most accurate for staging
• Not appropriate for surveillance
• Fibroscan requires ~$130,000 for machine
  • $300 per exam
  • Potentially portable by van
• Ultrasound with Elastography
  • <$300 per exam
  • Gives fibrosis level and provides a detailed ultrasound image
  • Not as well validated as Fibroscan but cheaper – adds $20 to a standard RUQ US
• Providence lab Fibrometer
  • $300 per test
Transducer

High-powered u/s pulse generates “shear waves” the velocity of which are measured

3cm

Velocity (V-m/s) of the waves is affected by elasticity (E-kPa) and are related by the formula $E = 3\rho V^2$. The stiffer the tissue, higher elasticity, the faster the waves travel.
While in this view the tech (Joel) selects those areas where the lines run the most in parallel. Speed measurements are taken from there. The faster the waves move, the wider the spaces between the lines.
Hep C Case #2

- 55 yo African American male
- Uses heroin intranasal now but prior IV use
- Hep C for at least 29 years
- Hx of Hep B and jaundice but told that he cleared it
- Prior Interferon/Ribavirin non-responder
- Told at that time he was cirrhotic
- Has not seen primary care in 10 years, recently re-established and now wants “Harvoni,” like on TV per referral
- Has RUQ pain, changes in appetite and weight loss
Hep C Case #2

- LFTs – AST 78, ALT 88, T Bili 2.1
- INR 1.5; Platelets 88; Albumin 2.7; AFP 78
- Genotype 3; HCV Qnt PCR 8 mill
- US with Elastography shows nodular appearance with F4 level fibrosis
- CT Dynamic Liver showed 3 < 3 cm masses in L lobe, Li-Rads 5 lesions = HCC
Hep C Case #2

- Not eligible for transplantation due to active substance abuse
- Resection candidate if he could get sober for 3 months
- Failed to respond to calls
- Presented to Providence ED in end-stage liver disease
- Placed on comfort care and passed
Hep C Case #3

- HCV Quant < 6mill
- Genotype 1a
- INR 2.2 due to Coumadin
- Platelets 212
- Albumin 3.8
- Total Bili 0.8
- Creatinine 1.8, BUN 34
- GFR 27
Current Hepatitis C Treatments

- **Genotypic**
  - Harvoni +
  - Viekira (triple therapy) *
  - Sovaldi
  - Daklinza
  - Zepatier *
  - Simeprevir

- **Pangenotypic**
  - Epclusa
  - Mavyret * + #
  - Vosevi (triple therapy) #

*Can be used in renal disease regardless of GFR
+ 8 weeks of treatment in non-cirrhotic patients
# No Ribavirin required in cirrhotic patients
Choosing a Drug

- Most choices are due to insurance coverage – formulary drug
- Prices are going down
- We predict this will be a Primary Care role in the next 12-36 months
Hepatitis E

- Fecal oral route majority with genotype 1, zoonosis in genotype 3, been found to be in zoonotic populations in the US – pigs particularly although boar (wild pigs) may be the more likely source – pig livers in particular have been linked, outbreaks in Europe have been linked to zoonotic sources but animal contacts at the time of outbreaks have been negative; in Japan and China genotype 4 has been found in animal reservoirs, once again there have not been found to be infected animals in contact with human subjects making it likely that this was person to person; more studies are being done to find the pathway to infection

- The Two Faces of Hepatitis E Virus; Hughes, Wilson, Teshale, Hu, Holmberg; Clinical Infectious Disease. 2010; 3: 328-334
Hepatitis E

- Incubation is 15-60 days, mean of 40 days
- Clinically manifests with icterus, malaise, anorexia, fever, hepatomegaly, and pruritus
- Lab findings of elevated bilirubin, markedly elevated levels of transaminases, and mild increases in alkaline phosphatase
- Can have no symptoms or fulminant hepatitis
- If Hep E is checked for IgM becomes detectable days before onset of symptoms and disappears during 4-6 month period
- Anti-HEV IgG appears soon after the IgM response and may persist up to 12 years after infection
- HEV RNA can be done through the CDC - found 2 weeks before to 1 week after onset of jaundice
- HEV RNA appeared in stool later than in blood and disappereed from stool in ~ 2 weeks after it became undetectable in blood

Transmission, diagnosis, and management of hepatitis E: an update; Santiago, Ramos, Mainardi, Gerona, and Arbiza; Hepatic Medicine. 2014; 6: 45-59
The Two Faces of Hepatitis E Virus; Hughes, Wilson, Teshale, Hu, Holmberg; Clinical Infectious Disease. 2010; 3: 328-334
Hepatitis E

- Pregnant women, immunocompromised patients, and children are at most at risk.

- Immunocompetent patients can get the acute hepatitis but it is more of a rarity, thought that elders and middle aged males are more at risk.

- Can be fatal - 0.2-4% fatality rate.

- Under tested for - has been linked to acute hepatitis with jaundice of unknown cause retrospectively.

- Extrahepatic manifestations have included acute pancreatitis, neurologic disorders including encephalitis, polyradiculopathy, Guillain-Barre syndrome, bilateral brachial neuritis, and proximal myopathy.

References:

Hepatitis E

- Vaccines are in development and preliminary human vaccine trials has been very effective

- Treatable – Ribavirin, Interferon, and Sovaldi (Sofosbuvir)

- Rare to have chronic infection in immunocompetent, but can be a significant issue in the transplant population

References:
- The Two Faces of Hepatitis E Virus; Hughes, Wilson, Teshale, Hu, Holmberg: Clinical Infectious Disease. 2010; 3: 328-334
Hep E Case

- 59 year old white male “foodie”
- Past medical hx significant for juvenile arthritis and psoriasis, takes Methotrexate + Folic Acid for the psoriasis/arthritis
- Recent travel to Provence, FRA
- Stayed in a farmhouse, ate locally prepared meats including pork
- Icterus started 1 week ago, last 3 days jaundiced with malaise
- RUQ pain and hepatomegaly on US and exam
- ALT 288, AST 312, T Bili 5.9, Alk Phos 189
Hep E Case

- For immunocompetent patients, treatment is the tincture of time, but in a patient with a hx of autoimmunity, may lead to chronic infection.
- Patient was noted to have peripheral neuropathy.
- Bilirubin came back to normal but had persistently elevated AST, ALT and mild elevation of alkaline phosphatase.
- After standard Hep A, B, and C tests were sent off, an autoimmune panel was sent off.
- ANA 1:125, AMA normal, F-Actin (anti-smooth muscle ab) normal.
Hep E Case

- Ferritin 469, Normal Iron and TIBC
- HEV considered and initial anti-HEV IgG was positive, anti-HEV IgM was negative; sample was sent off to CDC and HEV RNA was detected and titer of 6.2 x 10^{-5} iu/L, sequencing showed genotype 3.
- Started on Ribavirin 400 mg BID x 6 months
- Normalization of LFTs at month 2, RNA undetectable at month 4, and therapy stopped at month 6
- No recurrence of elevated LFTs
Questions....