Ask the Experts
Patient Education Program

Autoimmune Liver Diseases

Talal Adhami, M.D., HCMB.A., AGAF., FAASLD
April 26, 2017
LIVER FUNCTIONS

Liver is made of liver cells, with well defined functions, bile duct cells responsible for draining the bile, and eliminating cholesterol, toxins and certain metals.
Injury and Healing

- Immune system to heal and clean up and repair the injured site
- Immune systems is triggered by insult causes injury and cell death in normal cases
- Shuts off as soon as the repair process is over
Injury and Healing

• Autoimmune liver diseases occur when the immune system does not recognize a liver component as self and starts attacking it

• Injury, inflammation, cell death, liver dysfunction, healing scar tissue deposition (fibrosis) leading to cirrhosis
What is Autoimmune Liver Disease

• Autoimmune hepatitis is a long lasting disease

• Body's **immune** system attacks the liver and **causes** inflammation and damage (mainly scarring)

• Autoimmune hepatitis is a serious condition that may worsen over time if not treated.

• Autoimmune hepatitis can lead to cirrhosis and liver failure.
Disease Progression

- Normal Liver
- Chronic Hepatitis
- Cirrhosis
- HCC ESLD
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Disease Type and Treatment

• 4 major Categories
  • Autoimmune hepatitis (AIH)
  • Primary Biliary Cholangitis (PBC)
  • Primary Sclerosing Cholangitis (PSC)
  • Combination of the above

• Prevalence: 2-3/100,000
• Females (8x) >>>> male (except in PSC)

• Associated with other conditions
  – Thyroiditis
  – Rheumatoid Arthritis
  – Inflammatory bowel diseases
  – Vitiligo
Disease Type and Treatment

Treatment is effective especially in early stages (except PSC)

- Immunosuppression
- Bile Acid
- Liver transplantation
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Liver Transplantation

Teresa Diago Uso, M.D.
April 26, 2017
Milestones

1954 – kidney transplant
1966 – pancreas transplant
1967 – liver transplant
1981 – heart / lung
1983 – cyclosporin approved
1983 – single lung transplant
1983

Liver transplantation is approved as a therapeutic modality by NIH Consensus Conference
Transplants

![Graph showing trends in transplants over years, categorized by type of donor (deceased, living, all).]
Waiting time

Median months to transplant

Year of listing
Liver Transplantation

Liver transplantation should be reserved to those that have exhausted standard medical and surgical therapies.

Liver transplantation is a form of treatment, and as such was designed for those with life threatening complications of end stage liver disease.
## Complications of Liver Dysfunction and Cirrhosis

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal hypertension</td>
</tr>
<tr>
<td>- Esophageal varices</td>
</tr>
<tr>
<td>- Ascites</td>
</tr>
<tr>
<td>- Splenomegaly</td>
</tr>
<tr>
<td>Cardiovascular dysfunction</td>
</tr>
<tr>
<td>- Cardiomyopathy</td>
</tr>
<tr>
<td>- Hyperdynamic circulation</td>
</tr>
<tr>
<td>Pulmonary dysfunction</td>
</tr>
<tr>
<td>- Arterial hypoxemia from pulmonary shunts</td>
</tr>
<tr>
<td>- Pulmonary hypertension</td>
</tr>
<tr>
<td>Synthetic dysfunction</td>
</tr>
<tr>
<td>- Coagulopathy</td>
</tr>
<tr>
<td>- Hypoalbuminemia</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>- Hepatorenal syndrome</td>
</tr>
<tr>
<td>- Platelet dysfunction and coagulopathy</td>
</tr>
<tr>
<td>- Electrolyte disturbances</td>
</tr>
<tr>
<td>Neurologic dysfunction</td>
</tr>
<tr>
<td>- Hepatic encephalopathy</td>
</tr>
<tr>
<td>Excretory dysfunction</td>
</tr>
<tr>
<td>- Jaundice</td>
</tr>
<tr>
<td>- Pruritis</td>
</tr>
<tr>
<td>Risk of malignancy</td>
</tr>
</tbody>
</table>

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Indications for LTX

- Fulminant or sub-fulminant liver disease
  - Hepatitis B
  - Acetaminophen toxicity
  - Idiosyncratic drug toxicity
  - Hepatitis A
  - Adenovirus
  - Mushroom toxicity
  - Acute Wilson’s disease
  - Acute Budd-Chiari syndrome
  - Trauma or iatrogenic injury
  - Acute failure of previously transplanted liver
Indications for LTx

- **Chronic end-stage liver disease**
  - Chronic Hepatitis C
  - Non-alcoholic steatohepatitis (NASH)
  - Alcoholic liver disease
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Secondary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Biliary atresia
  - Cryptogenic cirrhosis
  - Chronic Hepatitis B
Indications for LTX

- **Metabolic liver disease**
  - Wilson’s disease
  - Alpha-1 antitrypsin deficiency
  - Hemochromatosis
  - Tyrosinemia
  - Hyperoxalosis
  - Familial polyneuropathy - amyloidosis
  - Crigler-Najjar syndrome

- **Malignancies**
  - Hepatocellular carcinoma
  - Metastatic neuroendocrine tumors
  - Hepatic Epithelioid Hemangioendothelioma
  - Cholangiocarcinoma
  - Metastatic colorectal cancer to the liver!!!!!
Waiting list by diagnosis

[Graph showing waiting list by diagnosis from 2004 to 2016, with categories like Acute liver failure, HCV, ALD, Chol. disease, Malignancy, Other/unknown.]
Contraindications for LTx

• Extrahepatic sepsis
• Advanced cardiopulmonary failure
• Multisystem organ failure
• Inability or unwillingness to comply with post-transplant medical therapy
• Active substance abuse?
• Advanced age (physiologic)?
• Extrahepatic malignancy (except for skin/colorectal)?
Model for End-Stage Liver Disease (MELD)

- MELD - predict mortality while waiting for LTx
- Based on four objective clinical lab values:
  Bilirubin, INR, creatinine, Na
UNOS regions
United Network for Organ Sharing
Waiting list by MELD score
3-Month Mortality Based on Listing MELD Score

MELD Score

Wiesner R. Gastroenterology 2003;124:91-96

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MELD Exceptions

- HCC
- Hepatopulmonary syndrome
- Cholangiocarcinoma
- Cystic fibrosis
- Familial amyloid polyneuropathy
- Portopulmonary hypertension
- Primary hyperoxaluria
UNOS criteria for OLT for HCC (Milan Criteria)

- Single tumor less than 5 cm
- Three or less tumors each less than 3 cm
- Absence of macrovascular invasion or distant metastases

Hepatocellular Carcinoma (HCC)

- The **most common primary liver malignancy**, the sixth most common cancer worldwide, and the third most common cause of cancer death.

- Affects 3.7 men per 100,000 per year and 2.0 women per 100,000 per year in the United States.

- Since the 1980s, the incidence of HCC in the US has tripled.

- The age distribution has shifted to a younger age: the greatest increases are in the age group 45 – 60 years old.

Elserag HB, Kanwal F. *Hepatology*. 2014; 60(5):1767-75
Management of Early HCC

- As outlined by the BCLC staging classification: Treatment options are defined by disease characters and functional capacity.
- Curative options for HCC include: Resection, RFA, and transplantation
- Resection is considered safe: Perioperative mortality is in the order of less than 1%, however outcomes are limited by the high recurrence rates.
- Transplantation is limited by the paucity of available organs.

Simplified management for HCC

1. HCC
   - Cirrhosis?
     - Yes: Portal hypertension Elevated bilirubin?
       - Yes: Transplant candidate (within Milan criteria)?
         - Yes: Liver transplant
         - No: Amenable to more LRT?
       - No: Locoregional therapy
     - No: Surgical resection (preferred) Or radiofrequency ablation if < 2-3 cm

2. Locoregional therapy
   - Downstaged into Milan Criteria?
     - Yes: Transplant candidate (within Milan criteria)?
       - Yes: Liver transplant
       - No: Amenable to more LRT?
     - No: Palliative care/sorafenib
LIVER TRANSPLANTATION FOR HCC (within Milan Criteria)

• 1 year survival 80-90 %

• 5 years survival 65-75 %

• Recurrence rates were 6.1%, 12.7%, and 15% at 1-, 3-, and 5- years respectively
Liver Transplantation

- Deceased donor
  - Whole
  - Split
- DCD donor
- Domino donor
- Living related donor
- HCV +ve donor
Left lateral, tri-segment split
LDLT vs. cadaveric graft

Advantages
• Assures a healthy organ with minimal preservation damage
• Independence from long cadaveric waiting list
• Optimizes the timing of transplantation
• Helps alleviate the severe shortage of cadaveric livers and death on the waiting list

Disadvantages
• Finite risk of donor morbidity and mortality
• Both operations are technically complex
• The program is extremely labor-intensive
• Reputational risk
Live donor liver transplantation

1988
Raia in Brazil is first to perform living donor liver transplant - mother to child but unsuccessful

1989
Strong and Lynch perform first successful LRD in Australia
Segmental Anatomy
Right liver graft
Survival
Future

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Current Developments in Treatment and Care

Stanley Martin Cohen, MD, FAAASLD, FACG
April 26, 2017
Liver Biopsy Without the Needle
(FibroSCAN or ultrasound elastography)

FibroScan slides courtesy of Sandhill Scientific, Inc.
FibroScan Advantages

• Easy to use
• FDA-approved
• Can be done by trained RN’s, MA’s, techs, etc
• Can be used to follow serial exams

• Amount of liver sampled:

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Baby Boomers Account for 70-80% of HCV

Estimated Prevalence by Age Group

Birth Year Group

Number With Chronic HCV Infection (millions)
The Centers for Disease Control and Prevention (CDC) has issued draft guidelines recommending a one-time anti-HCV antibody test for all baby boomers (those born from 1945 through 1965) in an effort to identify these undiagnosed individuals.
Chronic HCV Therapy (Genotype 1): Advances in Raising Cure Rates

<table>
<thead>
<tr>
<th>Year</th>
<th>治疗方式</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>IFN/RBV</td>
<td>16%</td>
</tr>
<tr>
<td>1998</td>
<td>IFN/RBV</td>
<td>35%</td>
</tr>
<tr>
<td>2001</td>
<td>PegIFN/RBV</td>
<td>44%</td>
</tr>
<tr>
<td>2011</td>
<td>PegIFN-Free Regimens</td>
<td>~70%</td>
</tr>
<tr>
<td>&gt;2015</td>
<td>2nd Generation DAAs</td>
<td>&gt;97%</td>
</tr>
</tbody>
</table>

IFN:干扰素  
IFN/RBV:干扰素-利巴韦林  
PegIFN: Peg干扰素  
PegIFN/RBV: Peg干扰素-利巴韦林  
Telaprevir or Boceprevir + PegIFN/RBV: 2nd Generation DAAs
## Hepatitis C

*(Advances in cure rates, genotype 1)*

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>Cure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir + Grazeprevir (C-EDGE)</td>
<td>95%</td>
</tr>
<tr>
<td>Sofosbuvir + Ledipasvir (ION1/3)</td>
<td>97-99%</td>
</tr>
<tr>
<td>Dasabuvir, Ombitasvir, Paritaprevir/ritonavir (Sapphire-1)</td>
<td>95%</td>
</tr>
<tr>
<td>Simeprevir + Sofosbuvir (Optimist)</td>
<td>97%</td>
</tr>
<tr>
<td>Sofosbuvir + Velpatasvir (Astral-1)</td>
<td>98%</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir (Ally-2)</td>
<td>96%</td>
</tr>
</tbody>
</table>
Curing Hepatitis C: The Benefits

• “Sustained viral response” or SVR or Cure
  
  – Durable
    • 99% stay HCV negative for >10 years

  – Biopsy can get better
  – Decreased risk of getting cirrhosis
  – Decreased risk of cirrhosis getting worse
  – Decreased risk of liver cancer
  – Decreased mortality
## Hepatitis B

<table>
<thead>
<tr>
<th></th>
<th>Peg-IFN 2a 180 mcg qwk 48 wk</th>
<th>Lamivudine 100 mg qd 48-52 wk</th>
<th>Adefovir 10 mg qd 48 wk</th>
<th>Entecavir 0.5 mg qd 48 wk</th>
<th>Telbivudine 600 mg qd 52 wk</th>
<th>Tenofovir 300 mg qd 48 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBV DNA</td>
<td>63%</td>
<td>60-73%</td>
<td>51%</td>
<td><strong>90%</strong></td>
<td>88%</td>
<td><strong>93%</strong></td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>38%</td>
<td>60-79%</td>
<td>72%</td>
<td>78%</td>
<td>74%</td>
<td>76%</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>59% (at 72 wks)</td>
<td>60-66%</td>
<td>64%</td>
<td>70%</td>
<td>67%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Fatty Liver and NASH

- The most common liver disease in the US

- Risk factors:
  - Obesity
  - Diabetes
  - High lipids (cholesterol/triglycerides)

- Treatments:
  - Weight loss, diet, exercise
  - Control of blood sugar
  - Control of lipids
  - ???????????????????????????????????????????????????????
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LIVER WELLNESS

Mousab Tabbaa, MD - ALF MAC Chair - President, North Shore Gastroenterology & Endoscopy Centers

April 26, 2017
THE 7 DA VINCIAN PRINCIPLES

1. Curiosità
   - An insatiably curious approach to life and an unrelenting quest for continuous learning.
   - Focus on questions!
   - Application and Exercises

2. Dimostrazione
   - A commitment to test knowledge through experience, persistence, and a willingness to learn from mistakes.
   - Application and Exercises

3. Sensazione
   - The continual refinement of the senses, especially sight, as the means to enliven experience.
   - “The five senses are the ministers of the soul.” - Leonardo
   - Application and Exercises

4. Sfumato
   - (literally “Going up in Smoke”). A willingness to embrace ambiguity, paradox, and uncertainty
   - “The painter who has no doubts will achieve little.” - Leonardo
   - Application and Exercises

5. Arte/Scienza
   - The development of the balance between science and art, logic and imagination. “Whole-brain” thinking.
   - Application and Exercises

6. Corporalità
   - The cultivation of grace, ambidexterity, fitness, and poise.
   - Application and Exercises

7. Connessione
   - A recognition of and appreciation for the interconnectedness of all things and phenomena. Systems thinking
   - Application and Exercises

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Patient perspective
LIVER WELLNESS = WELLNESS

• HEALTHY DIET:  *What to eat?*
  *Coffee?*
  *Alcohol?*

• EXERCISE:  *How much?*
  *What type?*

• Toxins:  *Polypharmacy?*
  *over-the-counters?*
  *Herbal supplements?*
DOCTOR PERSPECTIVE
Liver Wellness

• Understanding genetic makeup
• Addressing environmental factors
• Predicting response to environmental factors based on genetic makeup
• Predicting response to therapy and intervention
• Predicting side-effects (hepatotoxicity)
• Discovering pre-clinical “silent” injury
Definitions

**Pharmacogenomics (genetics):** Application of knowledge of genetic variation to predict therapeutic response or adverse events to a particular medication. Generally applies to germ line mutations (some apply to somatic mutations in tumor tissue)

**Personalized Medicine as it pertains to the field of PGx:** Right treatment in a right dose for right patient at right time.
Genetic variants

- Can modify treatment response
  - Some variants exhibit faster or greater response
  - Some variants exhibit less or no response

- Can predict or cause adverse drug reactions
  - Skin reactions
  - Drug induced liver injury
  - Hyperbilirubinemia
INCREASED BMI IS BAD FOR YOU!

- Coronary artery disease
- Hypertension
- Increased cholesterol and triglycerides
- Diabetes
- Atherosclerosis
- Strokes
- Peripheral vascular disease
- Dementia
- Fatty liver and Cirrhosis
- Arthritis
- Impotence
- Cancer of various organs
Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.
30% WORKOUT

70% DIET
EXERCISE
Effect of aerobic exercise training dose on liver fat and visceral adiposity


Journal of Hepatology, July 2015, Volume 63, Issue 1, Pages 174–182
Study Design

Fig. 1. Flowchart showing the study process. M, male; F, female; HI:LO, high intensity, low volume aerobic exercise; LO:HI, low to moderate intensity, high volume aerobic exercise; LO:LO, low to moderate intensity, low volume aerobic exercise; PLA, Placebo control group; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.
Study Conclusion

• All exercise doses (levels), irrespective of volume (minutes/week) or intensity (50-70% of maximum aerobic capacity) were effective in reducing liver fat and visceral adipose tissue by small but clinically important amount in previously inactive, overweight or obese adults.

• These changes were observed even without clinically significant weight loss.

• There was no difference between different exercise regimens for these benefits.
Exercise & Improvement of NAFLD: Practical Recommendations

• There is good quality evidence to support that regular exercise is beneficial in reducing the risk of NAFLD.

• Both aerobic and resistance training regimen are equally effective in reducing liver fat in individuals with NAFLD even in the absence of weight loss.

• There are no data to support that exercise alone without weight loss can improve or reverse NASH. Hence, lifestyle interventions utilizing both exercise and caloric restriction inducing weight loss (loosing approximately 5–10% of body weight) are needed to improve NASH.

• The United States Department of Health and Human Services exercise recommendations may lower liver fat but based upon our expert opinion more stringent exercise regimen coupled with dietary interventions may be needed to induce improvement in liver histologic features associated with NASH.

editorial by Loomba and cortez-Pinto
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Western dietary pattern and fast food

- Consumption of fructose, soft drinks, meat, saturated fat
- Consumption of fiber, PUFA, fish or omega-3 and vitamins

In one study > twice a week = 4.5 kg extra body weight = two fold greater insulin resistance

In other study: 18 healthy young students with at least 2 fast food meals a day for 4 weeks. 11 had elevated ALT at one week

- In clinical evaluations of subjects with elevated ALT

Questions about
- Alcohol and soft drink
- Recent excessive intake of fast food

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Mediterranean diet
ALCOHOL

Alcohol-related cancers

Injury

CVD

Respiratory

Coronary heart disease

Hazard rate ratio

g/day
Alcohol Consumption and the Risk of Cancer

A Meta-Analysis

Vincenzo Bagnardi, Ms.C., Marta Blangiardo, Ms.C., Carlo La Vecchia, M.D., and Giovanni Corrao, Ph.D.

- Alcohol consumption has been linked to an increased risk for various types of cancer.
- A combined analysis of more than 200 studies assessing the link between alcohol and various types of cancer (i.e., a meta-analysis) sought to investigate this association in more detail.
- This meta-analysis found that alcohol most strongly increased the risks for cancers of the oral cavity, pharynx, esophagus, and larynx.
- Statistically significant increases in risk also existed for cancers of the stomach, colon, rectum, liver, female breast, and ovaries.
- Concurrent tobacco use, which is common among drinkers, enhances alcohol's effects on the risk for cancers of the upper digestive and respiratory tract.
- The analysis did not identify a threshold level of alcohol consumption below which no increased risk for cancer was evident.
What do we recommend our patients with NAFLD about alcohol use?

• Heavy alcohol consumption has many harmful effects including those on liver and should be discouraged regardless whether an individual has NAFLD or not.

• Emerging epidemiological data suggest that light to moderate drinking may have favorable effects from a liver standpoint. But most studies are cross-sectional in nature and utilized surrogates such as aminotransferases and liver imaging.
What do we recommend our patients with NAFLD about alcohol use?

- Furthermore, it is not clear if cardiovascular and metabolic benefits of light to moderate alcohol consumption observed in general population are extended to those with NAFLD and NASH.
- There are emerging studies to suggest that even light alcohol consumption may increase the risk of cancers (e.g., breast and colon).
- *Until further data from rigorously conducted prospective studies become available, we believe that individuals with NAFLD should avoid alcohol consumption of any type or amount.*
COFFEE
Coffee consumption and liver function

• Drinking moderate amounts of coffee may help to reduce the risk of liver cancer, and the risk of developing liver cancer falls as coffee consumption rises.

• Moderate coffee consumption may also be related to a slower progression of liver disease. Patients with a higher coffee consumption have been found to display a milder course of fibrosis, especially in alcoholic liver disease.

• The association between moderate coffee consumption and a slower rate of fibrosis has also been seen in patients with hepatic fibrosis, cirrhosis, non-alcoholic liver disease and Hepatitis C.

• It is not yet clear whether, and to what extent, caffeine may be responsible for the reduction in risk of developing these diseases.

• Several different coffee components are being investigated. Kahweol and cafestol, naturally-occurring compounds in coffee, are being studied for their anti-carcinogenic effects, while the anti-viral properties of chlorogenic and caffeic acids are also under investigation.
• K Friedrich et al, 2016. Coffee consumption protects against progression in liver cirrhosis and increases long term survival after liver transplantation, Journal of Gastroenterology and Hepatology, published online ahead of print.
• O J Kennedy et al, 2016, Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis, Alimentary Pharmacology and Therapeutics, published online ahead of print.
• H Shen et al, 2016. Association between caffeine consumption and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Therapeutic Advances in Gastroenterology, Volume 9 (1).
DRUGS & LIVER INJURY

Etiology of Acute Liver Failure in the USA
Adult Registry (n = 2,224)

- APAP: 1025 (46%)
- Drug: 238
- Hep B: 159 (11%)
- Hep A: 37
- Autoimmune: 155
- Ischemic: 130
- Wilson’s: 28
- Budd-Chiari: 15
- Pregnancy: 20
- Other: 143
- Indeterminant: 274

ALF Study Group, Jan 2015

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Before

After

In only 6 weeks of drinking FitTea™ Robert lost $500
FATAL COMBINATION
The Ubiquity of Green Tea (Extract)
Liver Injury due to Green Tea Extract

- Over 50 reported clinical cases of liver injury
- No clear relationship between GTE dose and severity of liver injury (Navarro, 2009)
- Mechanism of injury conjectural
- Typical picture
  - Viral hepatitis like picture
  - Very high ALT elevations
  - Hepatocellular jaundice
Why is there risk of DILI from HDS?

- Inappropriate use
- Inherent toxicity
- Adulteration and contamination
- Herb-drug interactions
- Individual susceptibility