Immunizations and Medication Use in Cirrhosis: Which, How and When

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Objective

- Review cirrhosis and its natural history.
- Describe significance of immunizations in chronic liver disease.
- Understand the role of medications in chronic liver disease.
Cirrhosis

- End stage of any chronic liver disease
- Characterized histologically by regenerative nodules surrounded by fibrous tissue
- Clinically there are two types of cirrhosis:
  - Compensated
  - Decompensated
Cirrhotic liver

Nodular, irregular surface

Nodules

GROSS IMAGE OF A CIRRHOTIC LIVER
GROSS IMAGE OF A NORMAL AND A CIRRHOTIC LIVER

Normal

Cirrhosis

Irregular surface

Nodules
Normal

Cirrhosis

Nodules surrounded by fibrous tissue
Cirrhosis - Diagnosis

- Cirrhosis is a histological diagnosis
- However, in patients with chronic liver disease the presence of various clinical features suggests cirrhosis
- The presence of these clinical features can be followed by non-invasive testing, prior to liver biopsy
In Whom Should We Suspect Cirrhosis?

- Any patient with chronic liver disease
  - Chronic abnormal aminotransferases and/or alkaline phosphatase

- Physical exam findings
  - Stigmata of chronic liver disease (muscle wasting, vascular spiders, palmar erythema)
  - Palpable left lobe of the liver
  - Small liver span
  - Splenomegaly
  - Signs of decompensation (jaundice, ascites, asterixis)
In Whom Should We Suspect Cirrhosis?

Laboratory

- Liver insufficiency
  - Low albumin (< 3.8 g/dL)
  - Prolonged prothrombin time (INR > 1.3)
  - High bilirubin (> 1.5 mg/dL)

- Portal hypertension
  - Low platelet count (< 175 x1000/μl)

- AST / ALT ratio > 1
In Whom Should We Suspect Cirrhosis?

**Imaging studies**

- Liver-spleen scan
  - Small liver, irregular uptake
  - Splenomegaly
  - Colloid shift to bone marrow
- CAT scan / Ultrasound
  - Nodular liver
  - Splenomegaly
  - Venous collaterals
 Liver-Spleen Scan

**Normal**

**Cirrhosis**

- Small liver, irregular uptake
- Splenomegaly
- Colloid shift to bone marrow and ribs

**DIAGNOSIS OF CIRRHOSIS – LIVER-SPLEEN SCAN**
CAT Scan in Cirrhosis

Liver with an irregular surface

Collaterals

Splenomegaly
Confirmatory Liver Biopsy Is Not Always Necessary in Cirrhosis

- Liver biopsy is **not** necessary in the presence of any of the following:
  - Decompensated cirrhosis (**variceal hemorrhage, ascites, encephalopathy**)
  - Liver-spleen and/or CAT scan diagnostic of cirrhosis
- Liver biopsy is **not** necessary for pre-transplant evaluation
Optimal cutoff 8.74
Sensitivity 100%
Specificity 100%
Accuracy 100%
PPV 100%
NPV 100%

Optimal cutoff 0.31
Sensitivity 64%
Specificity 31%
Accuracy 43%
PPV 33%
NPV 62%

What is the Natural History of Cirrhosis?
Natural History of Chronic Liver Disease

Chronic liver disease → Development of cirrhosis → Compensated cirrhosis → Development of complications → Decompensated cirrhosis → Death

- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice
Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency

- Portal hypertension
  - Variceal hemorrhage
  - Ascites
  - Encephalopathy
  - Jaundice
- Liver insufficiency
Development of Complications in Compensated Cirrhosis

- Ascites
- Jaundice
- Encephalopathy
- GI hemorrhage

Probability of developing event:
- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

Months:
- 0
- 20
- 40
- 60
- 80
- 100
- 120
- 140
- 160

Gines et. al., Hepatology 1987; 7:122
Decompensation Shortens Survival

\[ \text{Survival (\%)} \]

\begin{tabular}{c c c c}
1-year & 2-year & 1-year & 2-year \\
Compensated & & Decompensated & \\
\end{tabular}

Decompensation Shortens Survival

Gines et al., Hepatology 1987;7:122

Median survival ~ 9 years

Median survival ~ 1.6 years

All patients with cirrhosis

Decompensated cirrhosis

Months

Probability of survival

Survival Times in Cirrhosis
## Child-Turcotte Score

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<th>Points</th>
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<td>1</td>
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<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>Good</td>
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<tr>
<td><strong>Bilirubin</strong></td>
<td>&lt;2</td>
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<tr>
<td><strong>Albumin</strong></td>
<td>&gt;3.5</td>
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- Child A: 5-6 pts
- Child B: 7-9 pts
- Child C: 10-15 pts
# Child-Turcotte-Pugh (CTP) Score

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<td>None</td>
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<tr>
<td><strong>PT (sec prolonged) or INR</strong></td>
<td>&lt;4</td>
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<td></td>
<td>&lt;1.7</td>
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<tr>
<td><strong>Bilirubin</strong></td>
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Child A: **5-6 pts**     Child B: **7-9 pts**     Child C: **10-15 pts**
Vaccine Preventable Hepatitis (VPH) in Patients Chronic Liver Disease (CLD)
Vaccine-Preventable Hepatitis (VPH)*: Basic Facts

*VPH includes hepatitis A (HAV) and hepatitis B (HBV); Hepatitis C is not vaccine preventable

- Acute illness from either virus can cause significant morbidity; chronic HBV infection is associated with mortality
- HAV is one of the most common vaccine-preventable diseases in international travelers
- HBV is the cause of up to 80% of hepatocellular carcinomas

Risk of Fulminant Hepatitis Following HAV Infection in Patients With CLD

- 595 Italian patients (mean age 29.1 years) with chronic HBV (n = 163) or HCV (n = 432) infection were prospectively monitored for 7 years.
- At analysis, 27 patients had acquired HAV, 17 of whom had chronic HCV.
  - 7 out of the 17 developed fulminant liver failure.
- None of the HAV cases in HBV group progressed to liver failure.

More Severe Complications Can Occur When HCV Patients Are Coinfected With HBV

- 92 consecutive patients with HCV seen in Hadassah Medical Center Liver Unit (Jerusalem)
- HBV coinfection observed in 66%
- Coinfection associated with more complications
  - Bleeding esophageal varices
  - Hepatic encephalopathy
  - Spontaneous bacterial peritonitis
  - Hepatocellular carcinoma

Immunogenicity of HAV Vaccine in Decompensated CLD Patients

HAV and HBV Vaccination Rates Are Low in Veterans with HCV

- MEDVAMC – serves >120,000 veterans
- HCV-infected patients were randomly sampled from VA data set between 2000 and 2005
  - Only 7.9% and 8.6% of the 3009 HCV-infected patients received hepatitis A and hepatitis B vaccinations, respectively
  - Only 6.5% and 8.2% of the subset of 275 HCV-infected patients with cirrhosis received hepatitis A and hepatitis B vaccinations, respectively

In this study there was significant underutilization of vaccination in patients with HCV

MEDVAMC=Michael E. DeBakey Veterans Administration Medical Center.
VPH Vaccination in Patients With CLD: Opinions in the Medical Literature

- Patients with CLD should be protected against VPH early in the natural history of their disease
  - Vaccine response in patients with mild-to-moderate CLD is similar to healthy subjects
  - The response to vaccination decreases in those with advanced disease or decompensated cirrhosis

Although patients with CLD may not be at increased risk of acquiring HAV or HBV, they may be at increased risk of complications if infected.

Patients with CLD may benefit from vaccination early in their disease course.
Medication Use in Cirrhosis

- Drug Induced Liver Injury (DILI)
- Role in GI Bleeding
- Effects on mental status
- Effects on renal and electrolyte balance
- Effects on hematologic status
Spectrum of Hepatotoxicity

- **Subclinical:** sulfonamides, salicylates, sulfonylureas
- **Acute hepatic injury:**
  - Cytotoxic – acetaminophen
  - Steatosis – amiodarone, AZT, ddi
  - Cholestatic – bactrim, rifampin
  - Extrahepatic – PCN, sulfa
- **Chronic cholestasis:** Intrahepatic (bactrim), biliary sclerosis (floxuridine)
Spectrum of hepatotoxicity (2)

- Granulomatous disease: amiodarone, sulfonamides, INH
- Chronic hepatic injury: chronic active hepatitis, steatosis (steroids, MTX, EtOH)
- Vascular disease: hepatic vein thrombosis (OCPs); SOS (herbs, OCPs, chemoTx); Peliosis hepatis (AZA, OCPs)
- Neoplasia: adenoma (OCPs); HCC (aflatoxin, alcohol)
Types of DILI

- Acute Injury – Hepatocellular & Cholestasis
- Chronic Injury – Steatohepatitis, Microvascular steatosis, Granulomatous hepatitis, Sinusoidal obstruction syndrome, Fibrosis, Peliois hepatitis, Autoimmune hepatitis, Chronic hepatitis
Acute Hepatocellular DILI

- Acarbose, acetaminophen, allopurinol, aspirin, bupropion, diclofenac, ethanol, fluoxetine, halothane, isoniazid, ketoconazole, lisinopril, losartan, methyldopa, nefazodone, nevirapine, paroxetine, phenytoin, pyrazinamide, rifampin, risperidone, ritonavir, statins, sertraline, tetracycline, trazodone, valacyclovir, valproate.
Acute Cholestasis DILI

- ACE inhibitors, amoxacillin/clavulanate, anabolic steroids, azathioprine, chlorpromazine, clopidogrel
Chronic DILI

- Steatohepatitis - amiodarone, ethanol, tamoxifen, valproic acid
- Microvascular steatosis – ethanol, MTX, NRTI, tetracycline, valproic acid
- Granulomatous – allopurinol, carbamazepine, diltiazem, hydralazine, phenytoin, procainamide, quinidine, rosiglitazone, sulfonamides.
- Sinusoidal obstruction syndrome – busulfan, cyclophosphamide, imuran
Chronic DILI

- Fibrosis – ethanol, MTX, methyldopa
- Peliosis hepatis – anabolic steroids, vinyl chloride
- Autoimmune – nitrofurantoin, minocyclin
- Chronic hepatitis – diclofenac, erythromycin, estrogens, ethanol, irbesartan, phenothiazine, sulindac, tricyclics.
Chronic DILI

- Mixed – amitryptilline, azathioprine, sulfonamides, phenytoin, nitrofurantoin
- Neoplasm – anabolic steroids, OCPs, vinyl chloride
- Ishemic necrosis - ergot
Classification of DILI

- Clinical/Laboratory – hepatocellular, cholestatic, mixed
- Mechanism – Direct, Idiosyncratic (immune-mediated, metabolic)
- Histologic findings – Cellular necrosis or apoptosis, cholestasis, fibrosis, granulomatous, sinusoidal obstructive syndrome VOD, phospholipoidosis
Herbal preparations with Hepatotoxic Potential

- Pyrrolizidine alkaloids: Crotolaria, Heliotropium, Mate’ (paraguay) tea; Senecio; Symphytum officinale (Comfrey); Ackee fruit; Atractylysis gummifera; Azadirachza indica; Berberis vulgaris; Callillepsis laureola; Cassia angustifolia; Cocaine (Erythroxylon coca) Cycasin; Pennyroyal; Chapparal, creosote bush, greasewood; Sassafras; Skull ccpp (Scutellaria); Germander (Teucrium Chamaedrys; Valerian; Mistletoe (Viscum Album)
Herbal preparations with Hepatotoxic Potential

Chinese herbal remedies and teas:

- Lycopodium serratum (Jin Bu Huan)
- Ma-huang
- Syo-saiko-to (Xiao-chai-hu-tang)
STATE SEeks HALIy OF PRODUCT SALES

Health officials are asking stores to pull from their shelves a dietary supplement tied to liver damage

By Sarah Zoellick
zoellick@staradvertiser.com

Twenty-nine confirmed cases, 11 hospitalisations, two liver transplants and one death later, the state Department of Health on Tuesday finally confirmed the name of the dietary supplement linked to a surge in acute liver inflammation and liver failure in the islands, asking that sale of the product come to a halt.

Health Department staff traveled store to store Tuesday appealing to local retailers to voluntarily remove all versions of the marketed “fat burner” OxyELITE Pro from their shelves while the agency continues to work with the Food and Drug Administration and Centers for Disease Control and Prevention.

Please see SUPPLEMENT, A8

ALARMING LINK

The OxyELITE Pro supplement, which users take for weight loss or building muscles, is suspected in a rash of cases of acute hepatitis and liver failure in Hawaii. It has been linked to 20 cases, including two liver transplants and one death since May, prompting state health officials to call on retailers to remove the product from store shelves.

NONVIRAL HEPATITIS

Hepatitis is an inflammation of the liver. Nonviral hepatitis is classified as toxic or drug-induced hepatitis. Most patients recover from this illness, although a few develop fulminating hepatitis or cirrhosis.

THE LIVER

The largest internal organ removes toxic wastes, helps the body absorb nutrients and makes clotting factors.

SIGNS AND SYMPTOMS

Clinical features of toxic and drug-induced hepatitis vary with the severity of liver damage and the causative agent. In most patients, symptoms resemble those of viral hepatitis:

• Loss of appetite
• Nausea
• Vomiting
• Jaundice
• Dark urine
• Hepatomegaly
• Abdominal pain
• Clay-colored stools

TREATMENT

Remove the harmful substance. Flush from the stomach or induce vomiting. Patients with drug-induced hepatitis may be prescribed corticosteroids.
Number of supplement users with liver damage grows

By Sarah Zoellick

As health officials are working with federal counterparts to track 30 cases

The number of people in Hawaii suffering liver damage linked to taking a dietary supplement for weight loss or muscle gain is now at 30, with the majority of cases on Oahu, state Department of Health officials said Wednesday.

There have been 21 cases reported on Oahu, seven on Hawaii Island, and one each on Kauai and Maui. The earliest of the cases goes back to May.

Eleven of the 30 patients have been hospitalized, two underwent liver transplants, and one died, DOH said.

The Maui patient, 48-year-old Sonnette Marras, died Oct. 4 after taking the dietary supplement OxyELITE Pro for several weeks to lose weight, she had gained during her last pregnancy, her family has said. Marras had seven children, ranging in age from 1 to 26.

According to an obituary notice released Wednesday, Marras worked as a construction laborer for Local 368 of the Laborers’ Union and also was a driver for Speddi Shuttle. She is survived by her companion, Michael Sortano; her mother, Gladys Marras; four daughters and three sons; and three brothers and three sisters.

The family declined to comment Wednesday, but before Marras died Sortano told Hawaii News Now that she was denied a liver transplant because doctors discovered a lump in her breast.

Speaking generally, Honolulu transplant surgeon Linda Wong said Wednesday that patients with active cancer do not receive organ transplants because anti-rejection medications can make cancer cells grow rapidly.

Wong said she has seen cases of liver damage and failure in the islands linked to dietary supplements before, maybe one or two a year, but that having so many in such a short time linked to a single product seemed unusual and was not statistically normal.

Other supplements that have caused people health problems over the years include but are not limited to Hydroxycut, Chinese herbs and slimming teas, Wong said.

“I think that there’s a lot of supplements that are being sold out there, and I think that people should tell physicians when they’re taking these things and they should report symptoms immediately and not wait too long before more severe symptoms happen,” she said.

Although DOH, the Food and Drug Administration and Centers for Disease Control, officially announced this week that OxyELITE Pro had been linked to 24 of the 30 cases of acute liver damage, the agencies still have not been able to pinpoint a precise cause for the epidemic. No cases have been reported in other states.

A spokesman for the FDA said Wednesday the agency is “working quickly to learn more” about which formulas of the weight loss and/or muscle gain supplement line were being taken by the affected patients and how a now-illegal formula of the product, which contains an ingredient known as DMAA (also known as 1,3-dimethylamylamine), was being purchased.

In the wake of the federal government shutdown that began Oct. 1, the FDA has been “doing what it can un-

Please see PILLS, B3
Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency

Cirrhosis → Portal hypertension → Varices → Variceal hemorrhage
Cirrhosis → Liver insufficiency → Varices → Ascites → Encephalopathy
Cirrhosis → Liver insufficiency → Varices → Jaundice
Varices are present in ~50% of patients with cirrhosis screened endoscopically at diagnosis.
Varices Increase in Diameter Progressively

No varices

Small varices

Large varices
Large varices have a higher risk of first variceal hemorrhage than small varices.

D’Amico et al., Sem Liv Dis 1999; 19:475
Combination Drug / Endoscopic Therapy is More Effective Than Endoscopic Therapy Alone

Sclero + Octreotide  Besson, 1995
Ligation + Octreotide  Sung, 1995
Sclero + Octreotide / ST  Signorelli, 1996
Sclero + Octreotide  Ceriani, 1997
Sclero + Octreotide  Signorelli, 1997
Sclero + ST  Avgerinos, 1997
Sclero + Octreotide  Zuberi, 2000
Sclero / ligation + Vapreotide  Cales, 2001

Pooled Relative Risk

Favors endoscopic therapy alone

Favors endoscopic plus drug therapy

Bañares R et al., Hepatology 2002; 35:609
Lowest Rebleeding Rates are Obtained in HVPG Responders and With Ligation + β-Blockers

Bosch and García-Pagán, Lancet 2003; 361:952

* ↓ HVPG <12 mmHg or >20% from baseline
Varices: Medications to Avoid

- Drugs that can cause direct mucosal injury to esophagus or stomach – Salicylates, NSAIDs, Bisphosphonates, Ethanol
- Drugs that can cause ischemic necosis like ergot or can cause Sinusoidal Occlusive Syndrome or VOD – OCPs, herbs, chemotherapy eg, 5FU etc
Management of Compensated Cirrhosis

- Screen for varices as soon as diagnosis is made (upper endoscopy, Pillcam?)
- Patients with large varices require prophylactic therapy for variceal hemorrhage with non-selective beta-blockers or EVL
- Patients with small varices require repeat endoscopy in 1-2 years
- Patients without varices require repeat endoscopy in 2-3 years
Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency

Cirrhosis

Portal hypertension

Liver insufficiency

Variceal hemorrhage

Ascites

Encephalopathy

Jaundice

Spontaneous bacterial peritonitis

Hepatorenal syndrome
Management of Decompensated Cirrhosis

Ascites

- Salt restriction
- Diuretics
  - Spironolactone alone
  - Spironolactone + furosemide
- Avoid NSAIDs
- No water restriction unless serum Na <130
- Low threshold to perform a diagnostic paracentesis to investigate SBP
- No antibiotic prophylaxis if no history of SBP
Post-Paracentesis Circulatory Dysfunction (PCD) Depends on the Type of Plasma Volume Expander and the Amount of Ascites Removed

Gines et al., Gastroenterology 1988; 94:1493; Gines et al., Gastroenterology 1996; 111:1002; Sola-Vera et al., Hepatology 2003; 37:1147
Management of decompensated cirrhosis
Spontaneous bacterial peritonitis

- Diagnostic paracentesis:
  - At admission
  - Development of symptoms/signs of SBP, encephalopathy and/or renal dysfunction

- Diagnosis based on ascites PMN count > 250/mm³

Management of Decompensated Cirrhosis
Spontaneous bacterial peritonitis

- **Systemic antibiotics**
  - Cefotaxime or ceftriaxone
  - Beta-lactam/beta-lactamase combination
  - Avoid aminoglycosides

- **Albumin in patients with any renal dysfunction at diagnosis**

- **Start long-term antibiotic prophylaxis (norfloxacin) upon discharge from hospital**
Norfloxacin Reduces Recurrence of Spontaneous Bacterial Peritonitis

Gines et al., Hepatology 1990; 12:716
Quinolones Administered Once a Week are not as Effective as Quinolones Administered Once a Day

Recurrent SBP

- Daily norfloxacin: 15%
- Weekly rufloxacin: 31%

Death

- Daily norfloxacin: 8%
- Weekly rufloxacin: 13%

Bauer et al., Dig Dis Sci 2002;47:1356
Management of decompensated cirrhosis

Hepatorenal syndrome

- Diagnosis of exclusion:
  - Sepsis
  - GI hemorrhage
  - Dehydration (prerenal azotemia)
    - Overdiuresis
    - Diarrhea
  - Nitrates or other vasodilators
  - Nephrotoxic substances (aminoglycosides, dye)
  - NSAIDs

- Persistence of renal insufficiency despite ruling out all of the above, diuretic discontinuation + albumin expansion
Management of decompensated cirrhosis
Hepatorenal syndrome

- **Treatment:** liver transplantation
- **Bridging therapy:**
  - Vasoconstrictors ([terlipressin](https://www.drugs.com/terlipressin.html), octreotide+miododrine, noradrenaline) + albumin
- **Therapy requiring further investigation:**
  - TIPS (in patients who have responded to octreotide + midodrine)
  - Extracorporeal albumin dialysis
- **Ineffective therapy:**
  - Dopamine
  - Hemodialysis
Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency

- Cirrhosis
- Portal hypertension
- Liver insufficiency

- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
Management of Decompensated Cirrhosis Encephalopathy

- Identify and treat precipitating factor
  - Infection
  - GI hemorrhage
  - Prerrenal azotemia
  - Sedatives
  - Constipation
- Lactulose (adjust to 2-3 BM/day)
- Short-term protein restriction (if at all)
Poor Correlation of Ammonia Levels With Presence or Severity of Encephalopathy

Ong et al., Am J Med 2003; 114:188
Treatment Options for OHE

- Reduction of nitrogenous load from gut
  - Bowel cleansing
  - Non-absorbable disaccharides (lactulose)
  - Antibiotics (rifaximin, metronidazole)*
  - Agents that bind NH$_3$ in the gut
    - Na benzoate
    - Na phenylacetate
    - Na hydroxybutyrate
- Drugs that affect neurotransmission (flumazenil, bromocriptine)
- Manipulation of splanchnic circulation (occlusion of portal-systemic collaterals)
  - Occlude TIPS shunt if present

* Neomycin (historical interest).
Antibiotics

- Activity against urea producing bacteria
- Inhibit production of ammonia
- Inhibit production of benzodiazepine-like ligands
- Neomycin -- 6 gm daily (3 divided doses)
  - Ototoxic, nephrotoxic
- Metronidazole -- 800 mg daily (1 week)
- Rifaximin -- 1200 mg daily
- Treatment of H pylori
Rifaximin Treatment in Hepatic Encephalopathy

Nathan M. Bass, M.B., Ch.B., Ph.D., Kevin D. Mullen, M.D., Arun Sanyal, M.D., Fred Poordad, M.D.,
Guy Neff, M.D., Carroll B. Levey, M.D.,* Samuel Sigal, M.D., Muhammad Y. Sheikh, M.D., Kimberly Beavers, M.D.,
Todd Frederick, M.D., Louis Teperman, M.D., Donald Hillebrand, M.D., Shirley Huang, M.S., Kunal Merchant, Ph.D.,
Audrey Shaw, Ph.D., Enoch Botrytis, Ph.D., and William P. Forbes, Pharm.D.

ABSTRACT

BACKGROUND
Hepatic encephalopathy is a chronically debilitating complication of hepatic cirrhosis. The efficacy of rifaximin, a minimally absorbed antibiotic, is well documented in the treatment of acute hepatic encephalopathy, but its efficacy for prevention of the disease has not been established.

METHODS
In this randomized, double-blind, placebo-controlled trial, we randomly assigned 299 patients who were in remission from recurrent hepatic encephalopathy resulting from chronic liver disease to receive either rifaximin, at a dose of 550 mg twice daily (140 patients), or placebo (159 patients) for 6 months. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy. The key secondary end point was the time to the first hospitalization involving hepatic encephalopathy.

RESULTS
Rifaximin significantly reduced the risk of an episode of hepatic encephalopathy, as compared with placebo, over a 6-month period (hazard ratio with rifaximin: 0.42; 95% confidence interval [CI], 0.28 to 0.64; P<0.001). A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.0% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group, for a hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P=0.01). More than 90% of patients received concomitant lactulose therapy. The incidence of adverse events reported during the study was similar in the two groups, as was the incidence of serious adverse events.

CONCLUSIONS
Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy. (ClinicalTrials.gov number, NCT00296038.)
Rifaximin 550 Treatment in HE
Conclusions

- Rifaximin 550 mg b.i.d. for 6 months reduced the risk of a breakthrough HE episode by 58% (NNT=4)
  - Xifaxan 550 mg reduction in risk of HE breakthrough was maintained across all subgroups
- Rifaximin 550 mg b.i.d. for 6 months reduced the risk of HE-related hospitalization by 50% (NNT=9)
- Xifaxan 550 mg b.i.d. had a safety profile comparable to that of placebo in patients with history of HE treated for up to 6 months

b.i.d. = twice daily; HE = hepatic encephalopathy; NNT = number needed to treat.
Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency
Management of decompensated cirrhosis

Jaundice

- No specific therapy
- Rule out the possibility of an “acute-on-chronic” disease
  - Alcoholic hepatitis
  - Drug hepatotoxicity
  - Biliary disease
- Accelerate transplant evaluation unless alcoholic hepatitis
Management of acute-on-chronic disease

Alcoholic Hepatitis

- Abstinence and nutritional support
- Of uncertain efficacy
  - corticosteroids: severe (DF>32 or HE)
  - pentoxifylline, infliximab
  - MARS
- Of no efficacy:
  - anabolic-androgenic steroids
  - propylthiouracil
Natural History of Chronic Liver Disease

- Development of cirrhosis
  - Chronic liver disease
  - Compensated cirrhosis
  - Development of complications:
    - Variceal hemorrhage
    - Ascites
    - Encephalopathy
    - Jaundice
  - Decompensated cirrhosis
    - Orthotopic liver transplant (OLT)
- Death
Mahalo
A Hui Hou
Aloha!!!
Thank you
Till we meet again