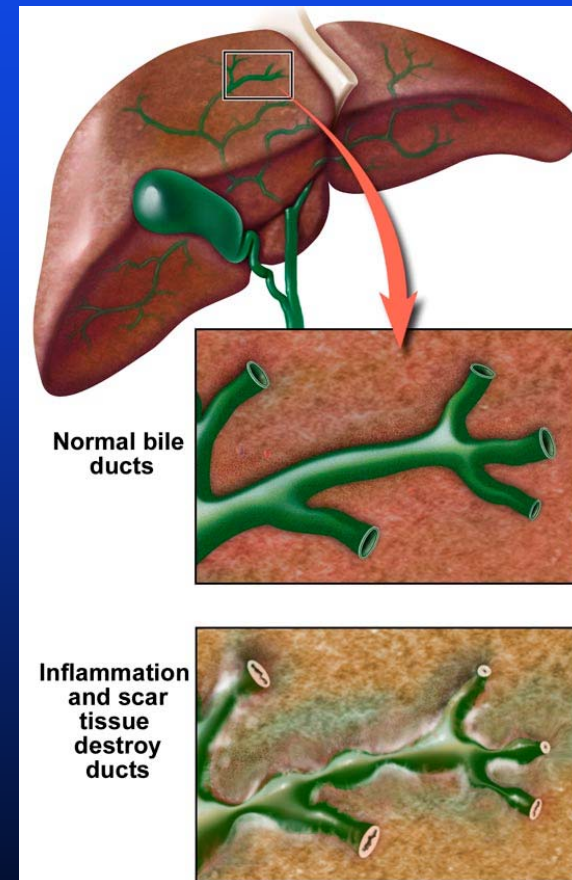


Primary Sclerosing Cholangitis Medical Management

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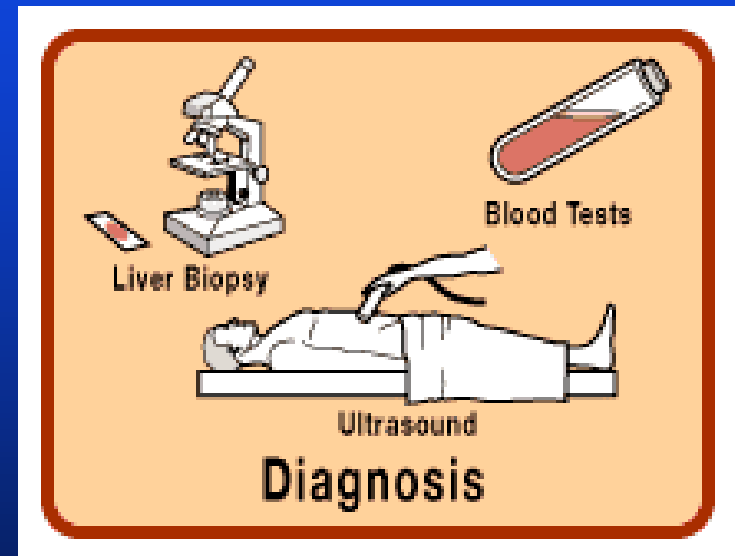
PSC

- **Primary sclerosing cholangitis is a progressive chronic cholestatic liver disease of unknown etiology that is commonly associated with chronic colitis**
- **PSC usually leads to advanced liver disease and liver failure, and is an important indication for liver transplantation**
- **Unfortunately, no effective medical therapy currently exists for PSC**



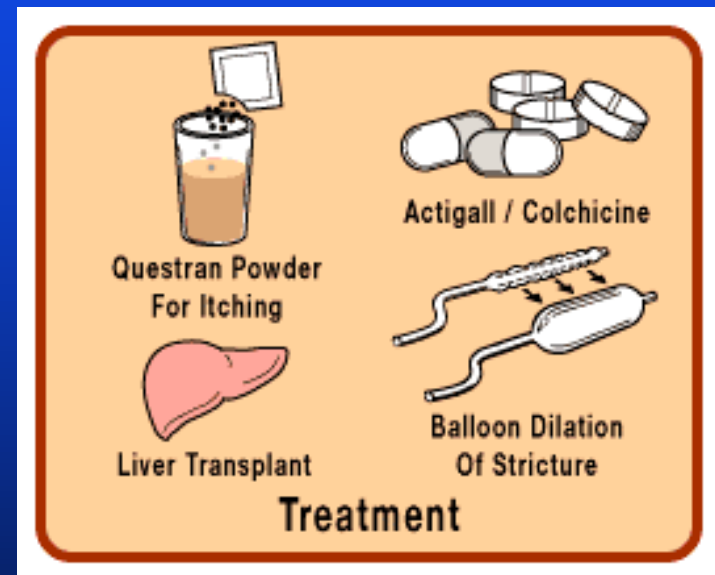
Diagnosis of PSC

- **PSC – first suspected after an abnormality appears in a routine blood test evaluation**
- **Most specialists use blood tests, cholangiography and liver biopsy to diagnose PSC**
- **Many patients have no symptoms and may remain symptom-free for years**



Management of PSC

- Management of Complications
- Specific Therapy for PSC
- Medical Therapy
- Liver Transplantation



PSC: Mayo Risk Score

- To estimate patient survival in PSC
- $R = 0.03 (\text{age [yrs]}) + 0.54 \log_e (\text{bilirubin [mg/dl]}) + 0.54 \log_e (\text{AST [u/l]}) + 1.24 (\text{variceal bleeding [0=no/1=yes]}) - 0.84 (\text{albumin [g/dl]})$
- Used to obtain survival estimates upto 4 years of follow-up
- Obviates the need for a liver biopsy

Kim WR et al. *Mayo Clin Proc* 2000;75:688-694
<http://www.mayoclinic.org/gi-rst/mayomodel3.html>

Complications of PSC

- Due to:
 - **Decompensated cirrhosis and portal hypertension**
 - **Chronic cholestasis**
- **Specific for PSC**

PSC: ***Chronic Cholestasis***

- Pruritus
- Fat-soluble vitamin deficiency
- Metabolic Bone Disease
- Hyperlipidemia
- Steatorrhea

PSC: ***Fat-soluble Vitamin Deficiency***

- Vitamins A, D, E, K
- ***Common – as patient progresses toward liver transplantation***
- Vitamin A deficiency: **40 %**
- Vitamin D deficiency: **14 %**
- Vitamin E deficiency: **2 %**

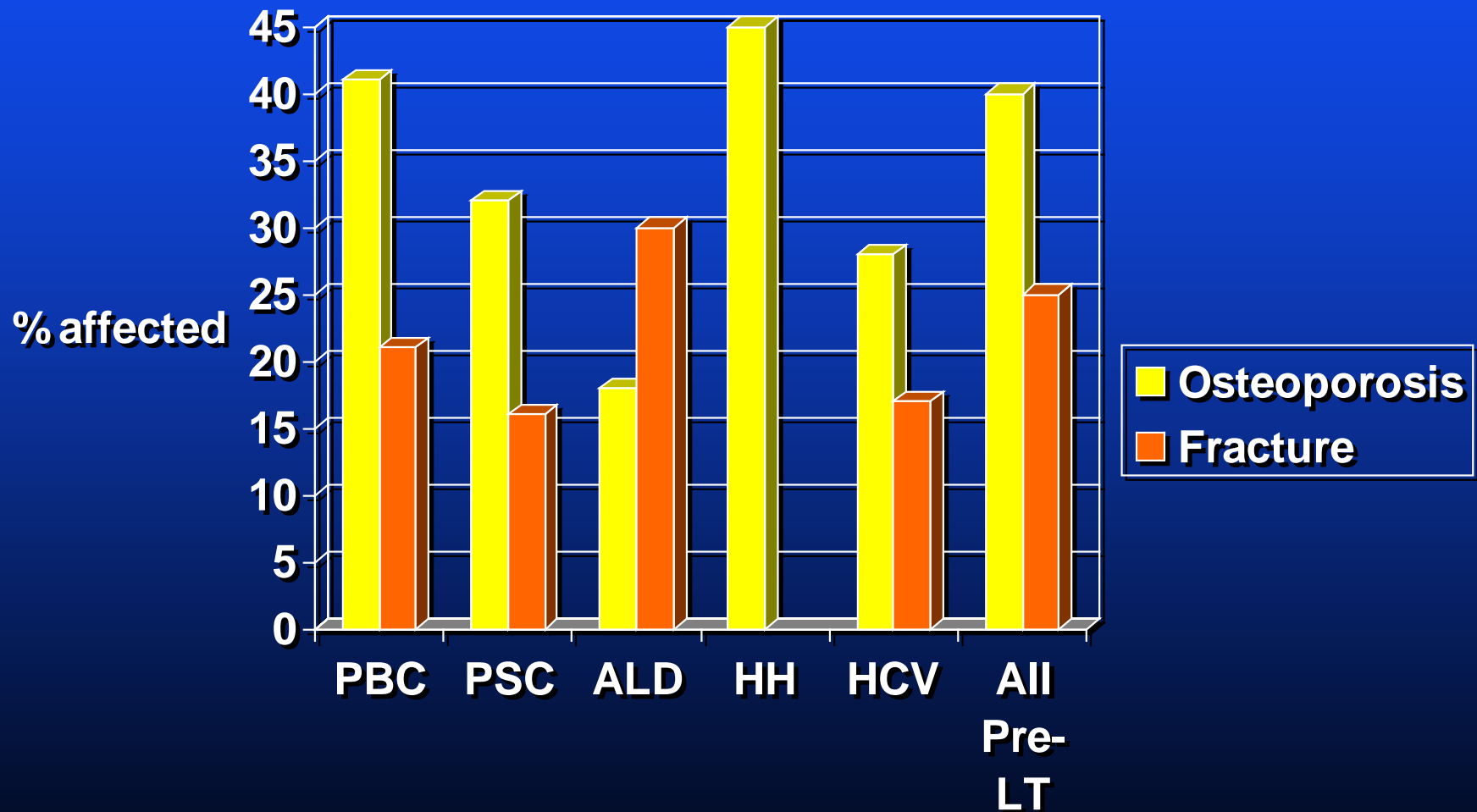
PSC: *Fat-soluble Vitamin Deficiency* **Replacement Therapy**

- **Vitamin A**
 - 25-50,000 units 2-3 times per week
- **Vitamin D**
 - 25-50,000 units 2-3 times per week
- **Vitamin E**
 - 100 units twice daily
- **Vitamin K**
 - 5 mg daily

PSC: *Metabolic Bone Disease*

- Common ~ 38 %
- Osteoporosis – advanced PSC
- Osteopenia in lumbar spine, iliac crest and femur
- Glucocorticoids used to treat IBD aggravate the osteoporosis
- After liver transplantation – prone to develop fractures

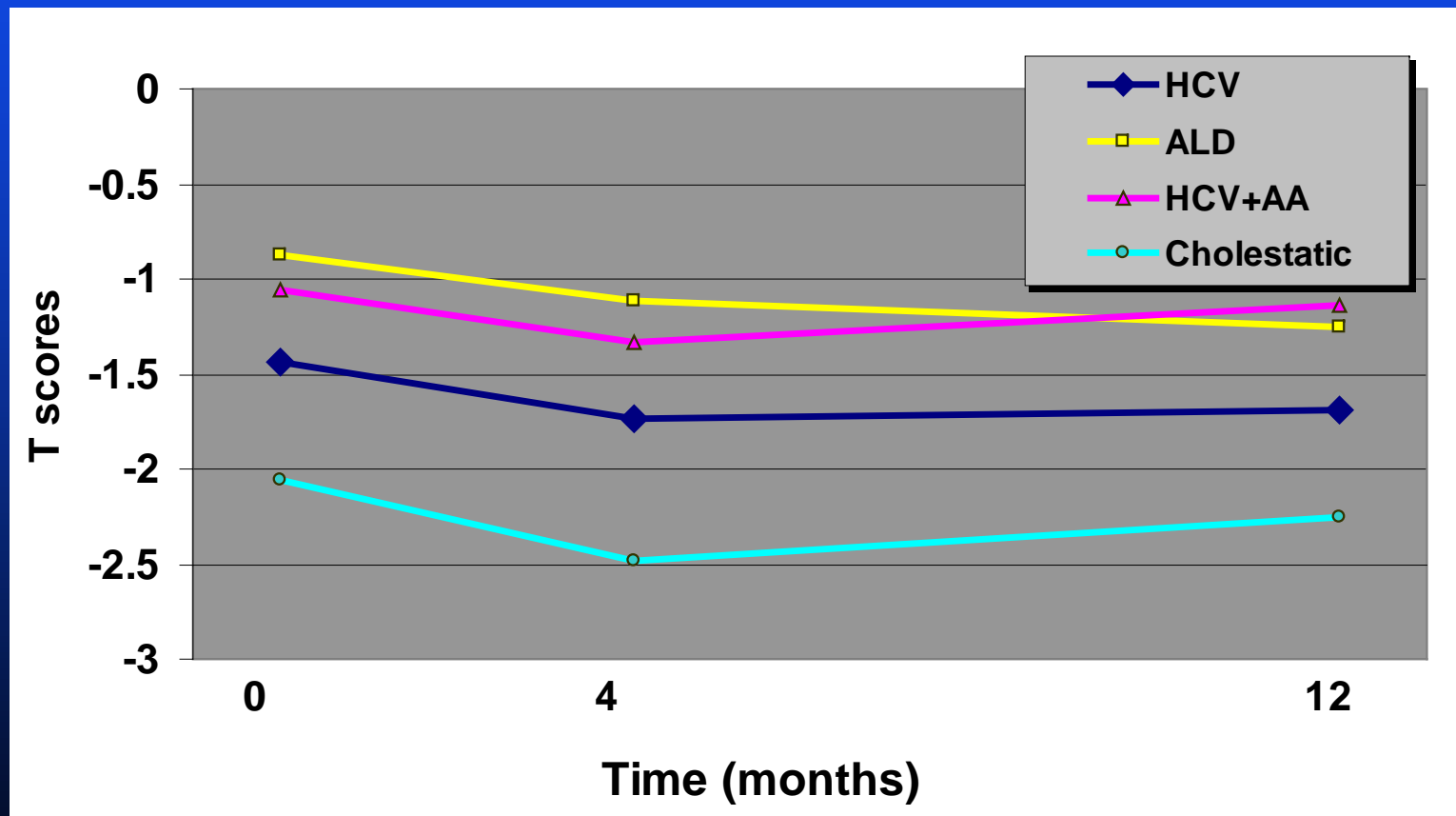
Osteoporosis and Fracture in Patients with Advanced Liver Disease



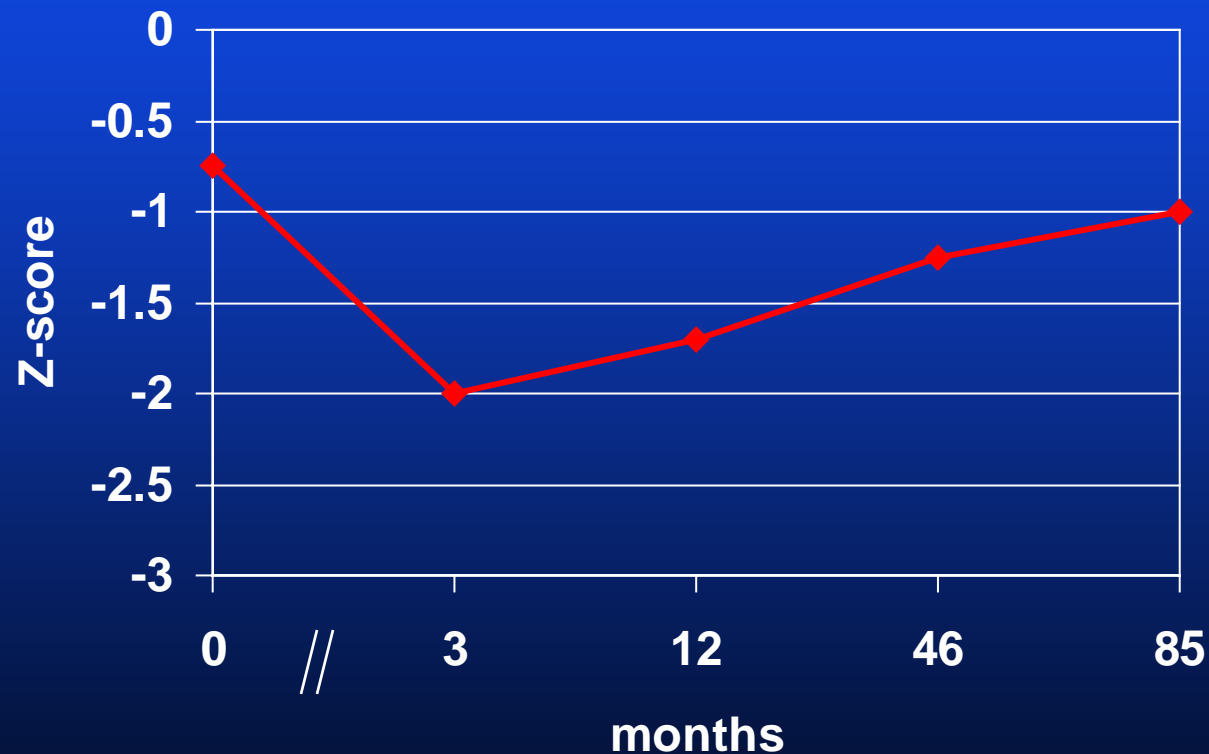
Definitions

- | | <u>T score</u> |
|----------------|----------------|
| • Normal | > -1.0 |
| • Osteopenia | -1 to -2.5 |
| • Osteoporosis | < -2.5 |
- T score: Number of standard deviations from the mean for young gender matched adults
 - Z score: Number of SD from the mean for age and gender matched adults

LS T-Scores in Patients with HCV, ALD, HCV+ALD, and PSC/PBC



Bone Recovery Continues for up to 7 Years Post-LTx



Factors Contributing to Osteoporosis in Liver Disease

Liver Disease

- Tobacco abuse
- Alcohol abuse
- Cholestasis
- Hypogonadism
- Drugs

Transplantation

- Immobility
- Corticosteroids
- Malnutrition
- Reduced muscle mass/low BMI
- Hormone fluctuation
- Immunosuppression

Management of Osteopenia

- **General Recommendations**

- Tobacco, caffeine, excess alcohol avoidance
- Weight-bearing exercise
- Ideal body weight
- 1500 mg Calcium + 400-800 IU Vitamin D
- Thyroid and gonadal status

- Hormone Replacement Therapy
- Calcitonin
- Bisphosphonates
- Alendronate
- Zolendronic acid
- Anabolic agents
 - Fluoride
 - PTH

PSC: Specific Complications

- **Gallstones**
- **Biliary Strictures**
- **Cholangiocarcinoma**
- **Varices**

Varices

- **Peristomal varices – in patients with ileostomy after proctocolectomy for underlying IBD**
- **Bleeding can be severe/refractory**
- **Therapy: local measures; ileostomy revision; injection of sclerosants**
- **Shunt: TIPS or portacaval shunt**
- **Consider Liver transplantation**

PSC: Surgical therapy

- **Surgical therapy other than liver transplantation – seldom warranted**
- **? Biliary reconstruction (not been validated)**
- **Nontransplantation surgery – for extensive extrahepatic dominant strictures**

PSC: **Medical Therapy**

- Variety of ***immunosuppressive*** and ***anti-inflammatory*** agents studies
- None – conclusively proven to alter the natural history of PSC
- ? High-dose Ursodeoxycholic acid (UDCA)
– randomized trial currently underway

PSC: Medical Therapy

Therapies tested to date

- **Penicillamine**
- **Cyclosporine**
- **Nicotine**
- **Colchicine**
- **Methotrexate**
- **Budesonide**
- **Pirfenidone**
- **Azathioprine**
- **Ursodeoxycholic acid**
- **Mycophenolate mofetil**

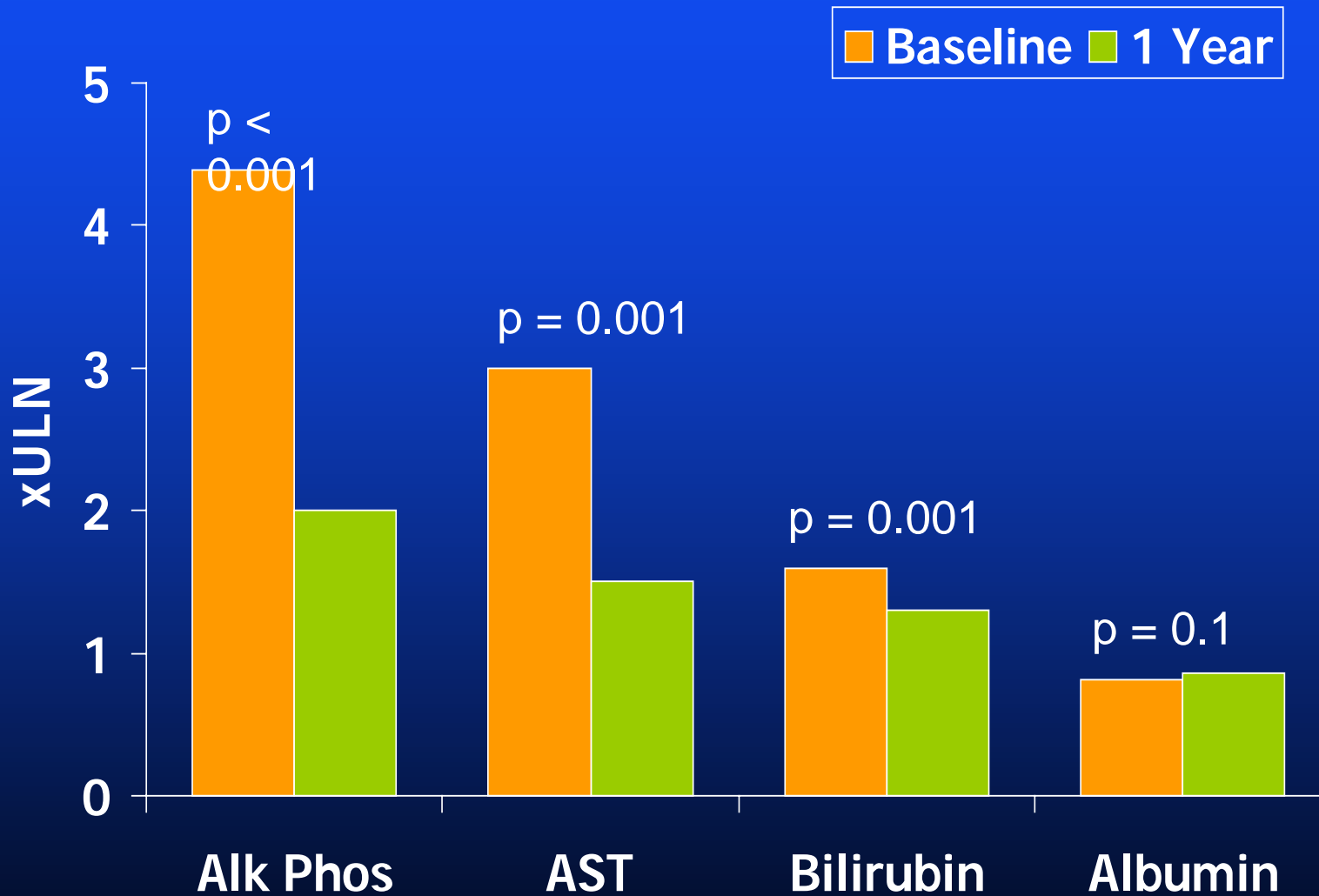
Ursodeoxycholic acid (UDCA)

- **Improves biochemical abnormalities**
- **Stabilizes hepatic inflammation**
- **Does not result in a survival benefit**
- **Does not delay need for liver transplantation**
- **Not able to prevent development of biliary strictures**

PSC: High dose UDCA

- **High dose UDCA (20 to 30 mg/kg/day)**
- **Two pilot studies**
- **30 patients treated for one year**
- **23 patients completed study**
- **Liver biochemistries and Mayo risk scores improved significantly**
- **Estimated – an expected decrease in mortality at four years from 17 to 11 %**

High Dose UDCA for PSC



PSC: High dose UDCA

- 26 patients randomly assigned to high dose UDCA (20 mg/kg/day) or placebo
- Two year follow-up
- UDCA treatment associated with
 - improvement in *liver biochemistry*
 - reduction in progression on *cholangiography* and *liver fibrosis*

PSC: High dose UDCA

- **Randomized placebo-controlled study; five years**
- **219 patients (UDCA = 110; placebo = 109)**
- **UDCA (17 to 23 mg/kg/day)**
- **No differences in symptoms or quality of life**
- **No differences in rates of liver transplantation; cholangiocarcinoma and liver failure**

PSC: High dose UDCA Research Study

- **Multi-center placebo-controlled randomized trial - minimum follow-up of four years for 150 patients with PSC**
- **This study will be the largest ever conducted in PSC and the follow-up will be the most extensive**
- **This will provide an invaluable resource for studying the natural history of this disease**
- **As part of this study collection of serum, cells for extraction of DNA, bile, and tissue from the liver and colon will serve as a resource for future studies**
- **The multi-centered nature of this trial will allow recruitment of patients into this study from a diverse patient population, representative of the gender and racial distribution of this disease**

PSC: High dose UDCA Research Study

- ***Primary endpoints***
 - histologic progression to cirrhosis
 - development of esophageal or gastric varices
 - need for liver transplantation
 - survival
- ***Secondary endpoints*** include measurements of the effects of ursodeoxycholic acid (28-30 mg/kg/d) on
 - liver biochemistries
 - histologic stage
 - cholangiographic features
 - Mayo risk score
 - quality of life

PSC: **Corticosteroids**

- **No long-term benefit**
- **Used either alone or in combination with colchicine**
- **Oral Budesonide: improvement in alkaline phos; no change in Mayo risk score; femoral neck bone loss**

PSC: **Other Therapies**

- Cyclosporine
- Methotrexate
 - Methotrexate + UDCA
- Azathioprine
- Tacrolimus
- Penicillamine
- Etanercept

PSC: **Other Therapies**

- **Combination therapy**
 - **Azathioprine + prednisolone + UDCA**
 - **Budesonide + UDCA**
 - **Prednisone + UDCA**
- **Antibiotics**
 - **Metronidazole + UDCA**

PSC: Minocycline

- **NO is produced by inducible nitric oxide synthase (iNOS), which is known to be upregulated in PSC, potentially contributing to the chronic inflammation and malignant transformation**
- **Minocycline, which by inhibiting iNOS activity, potentially reduces the inflammation of the bile ducts**
- **Open-label pilot study for 12 months**

PSC: Preventive Medicine

- **Hepatitis A vaccination**
- **Hepatitis B vaccination**
- **Influenza vaccination**
- **Pneumococcal vaccination**

PSC and Colorectal Cancer (CRC)

- Increased risk of CRC in patients with ulcerative colitis (UC) + PSC
- Risk increased by **fourfold** in patients with UC + PSC (compared to UC alone)
- All PSC patients without a prior diagnosis of IBD – flexible sigmoidoscopy/random rectal biopsies

PSC and Colorectal Cancer (CRC)

- PSC + UC: **annual colonoscopic surveillance**
- Use of UDCA associated with lower frequency of colonic dysplasia in UC + PSC
- Incidence of CRC increased in patients with UC + PSC after liver transplantation

Autoimmune Pancreatitis

- Cholangiographic appearance may be indistinguishable from that of PSC
- Although initially described in Japan, it has been reported worldwide
- **Elevated IgG 4** is characteristic
- It may present as pancreatic mass. Pancreatic insufficiency in the absence of gland atrophy or ductal dilation on CT may provide a clue to the diagnosis
- **Prednisone** 30-40mg daily has resulted in dramatic improvement including resolution of cholangiographic abnormalities.
- Response may be limited in patients with cirrhosis.

Thank You

