The Basics: PSC 101

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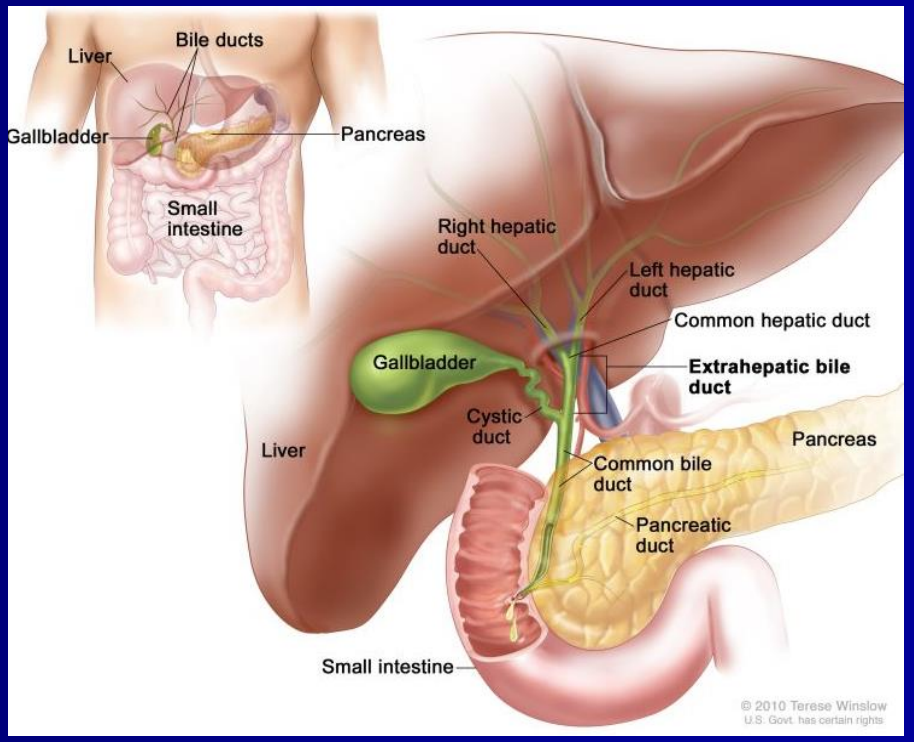
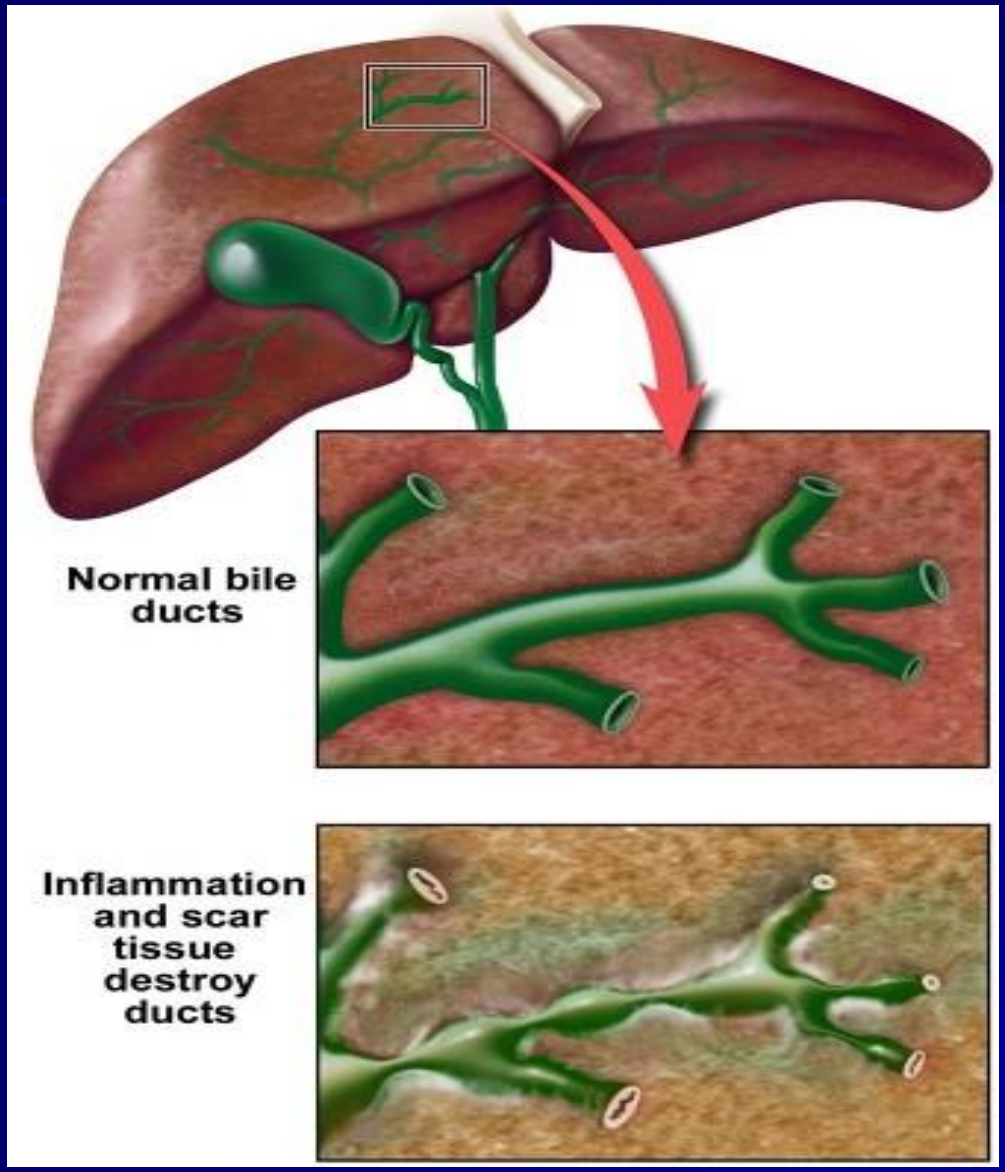
The Liver has Many Functions

- Makes sugar
- Detoxifies
- Makes clotting factors
- Makes bilirubin
- Makes protein

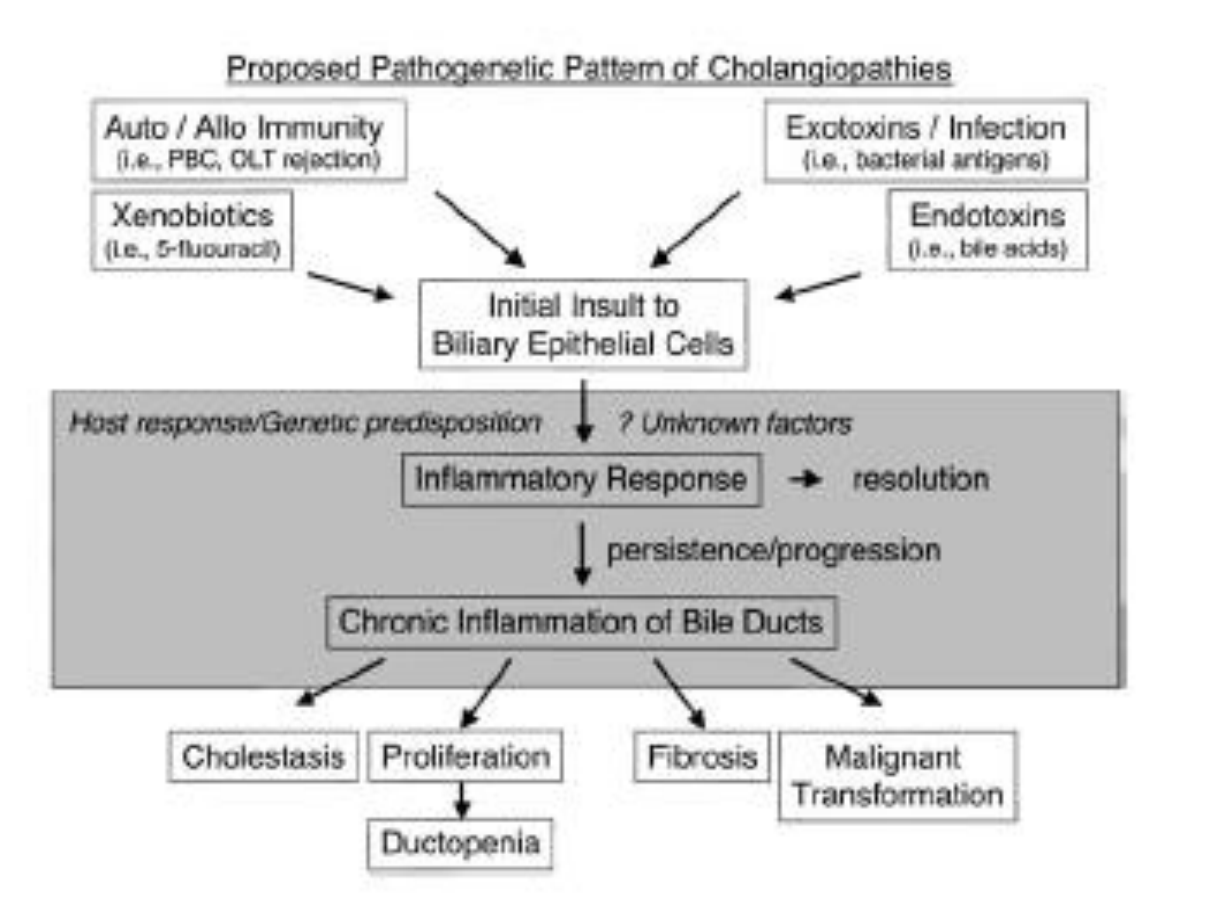


Primary Sclerosing Cholangitis

Inflammation and destruction of intrahepatic and extrahepatic bile ducts (cholangitis). This leads to segmental scarring and strictures (sclerosing)


Normal bile ducts
Inflammation and scar tissue destroy ducts

Pathogenesis



Epidemiology

- Incidence 0.5-1.3 per 100,000
- Males>Females
- Young-middle aged; average 40
- Wide geographic variation
  - Northern Europe, North American, New Zealand
- Strong association with IBD, esp UC
  - 70-80% have UC
  - 2-7.4% with UC and 1.5-3.5% with CD will dvlp PSC

Typical Symptoms

- Itching
- Fatigue
- Yellow eyes
- Weight loss
- Malaise
- Pain
- Fever
- Asymptomatic

Labs

- Elevated alkaline phosphatase
- ALT and AST often 2-3x higher than normal
- Bilirubin usually normal at diagnosis
- Liver function tests (LFTs) can be normal, and fluctuate during course
- Need to exclude other liver disease
- Need to exclude secondary causes (infection, trauma)

Labs

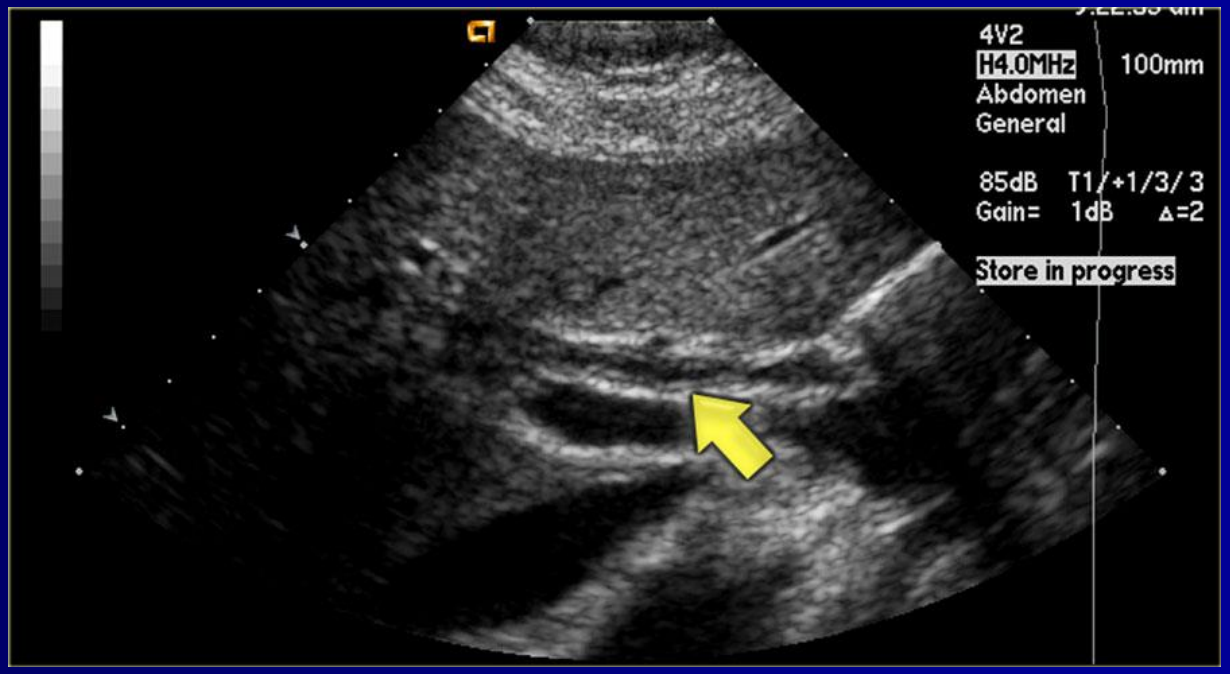
- Autoimmune markers may be present
  - pANCA
  - ANA
  - ASMA
  - IgG4

Diagnosis: Radiographic Tests

- MRI
- CT
- Ultrasound
- Cholangiogram
  - ERCP
  - PTC

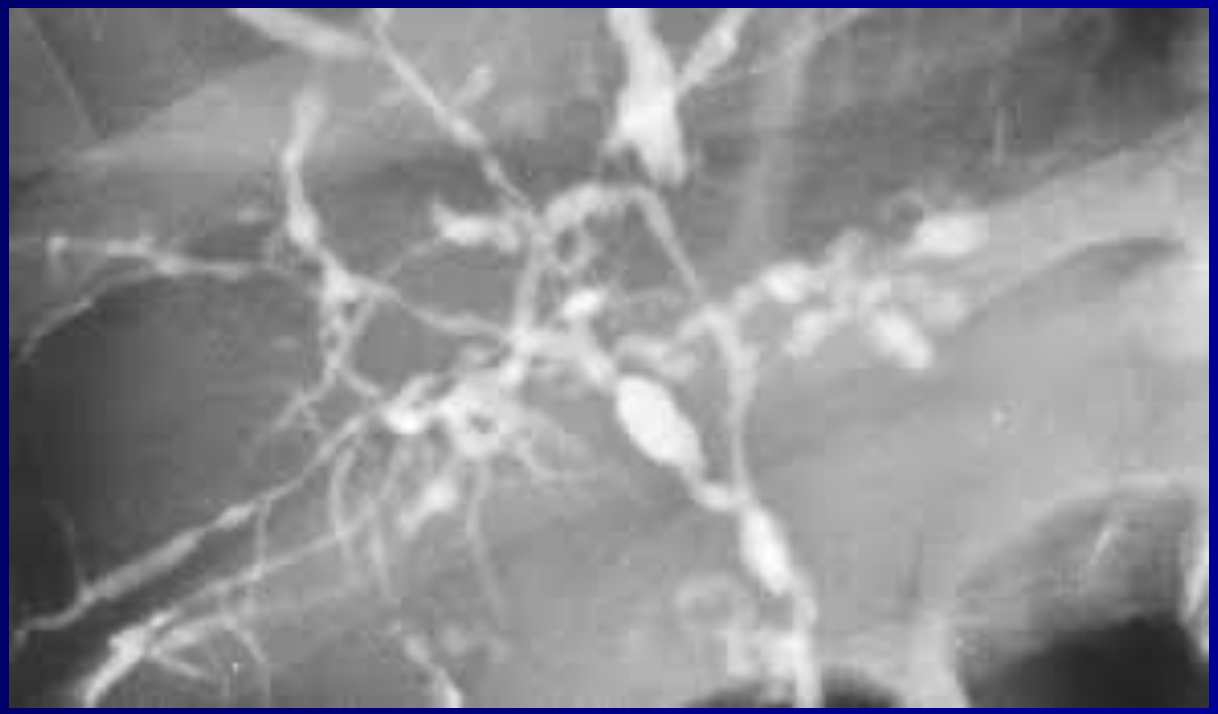
Ultrasound

- Often normal
- Thickened bile ducts

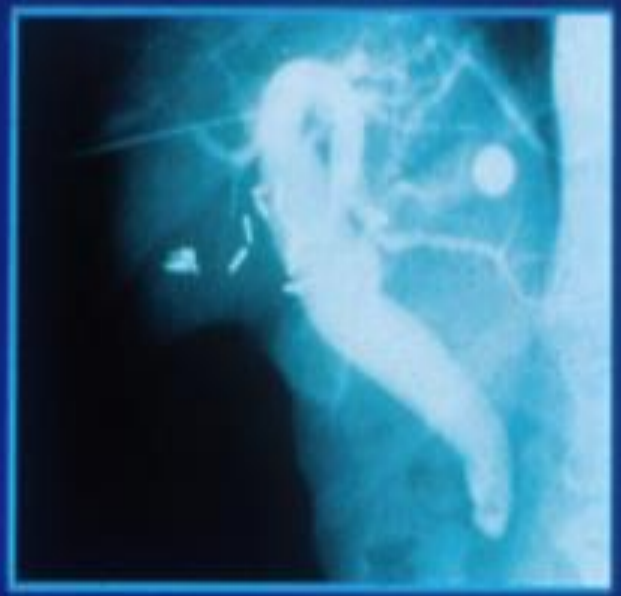


Endoscopic Retrograde Cholangiopancreatography

- Diagnostic of PSC
- Multiple strictures and dilations of bile ducts



PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY



ADVANTAGES

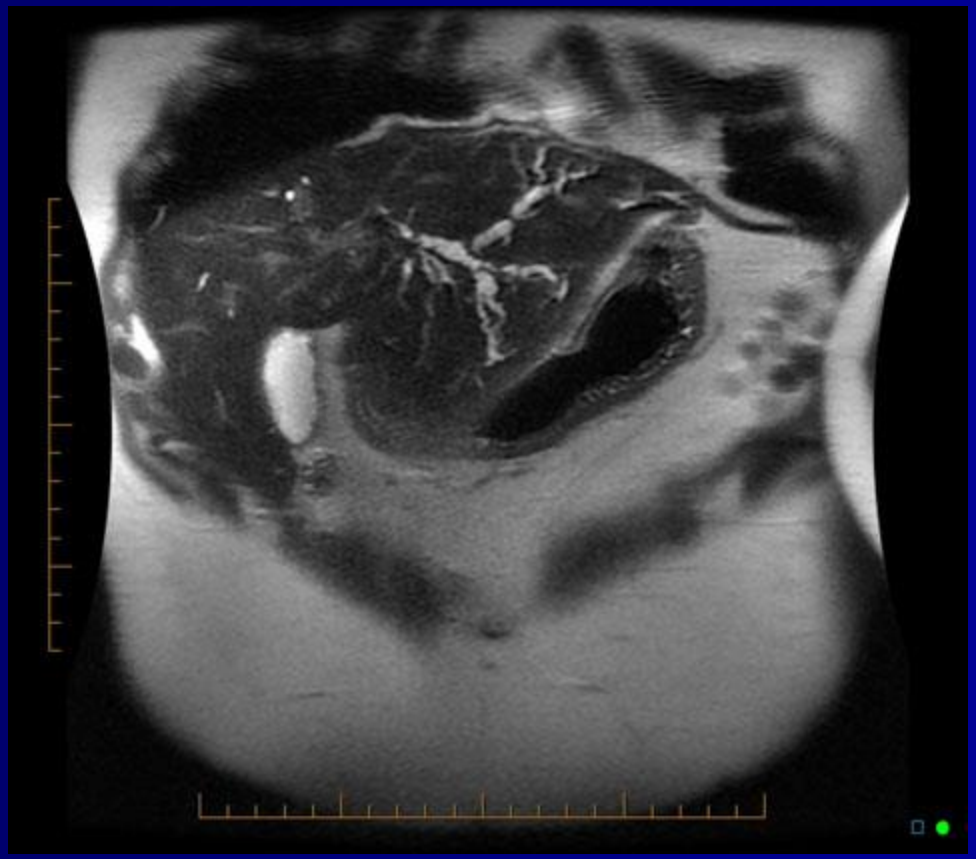
- Direct visualization of bile ducts
- Proximal extent of obstruction/lesion
- Therapeutic options: stenting
  stricture dilatation
- Less operator dependent than ERCP

LIMITATIONS

- Pancreatic duct not seen
- Biliary-venous connection
- Complications: sepsis
  bile leak
- Success related to duct size

Magnetic Resonace Cholangiopancreatography

- Focal thickening and dilation of bile ducts

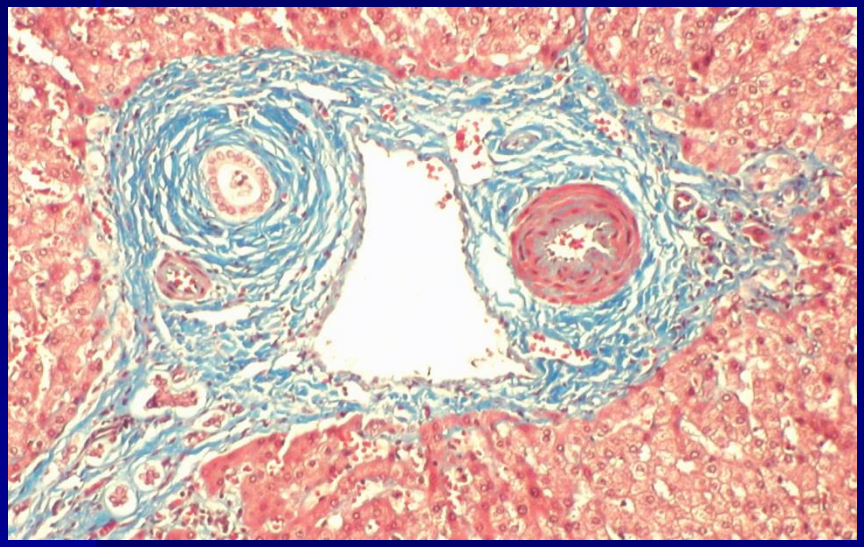


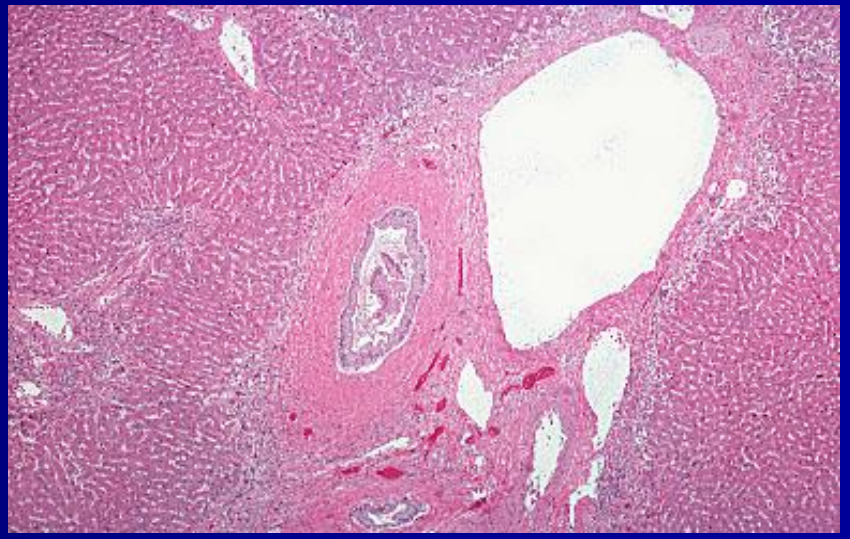
Liver Biopsy

- Exact role undefined
- Primary injury is not liver cells but medium and lg bile ducts
  - not captured in typical bx
- "onion skin" fibrosis around bile ducts

- May help exclude other diseases

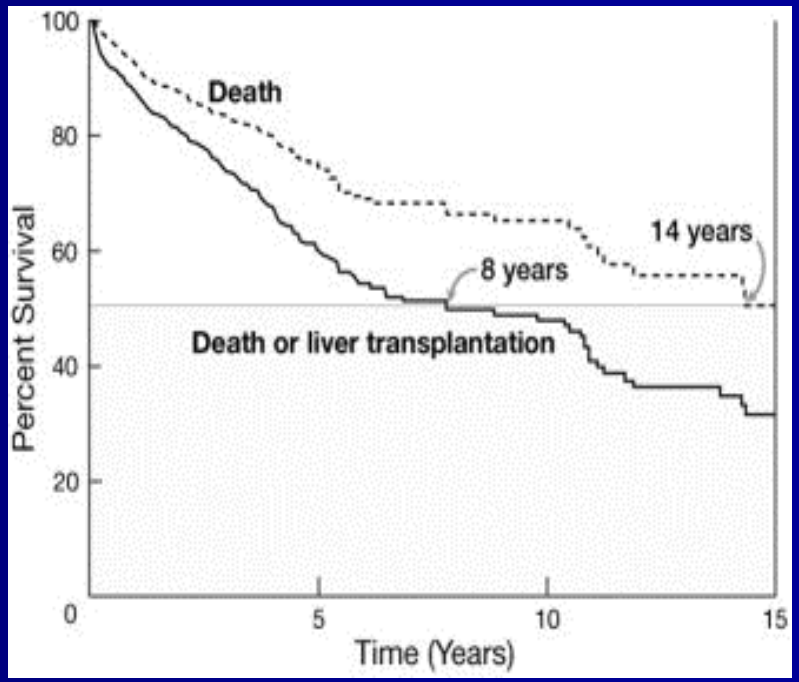
Liver Biopsy: Onion Skin



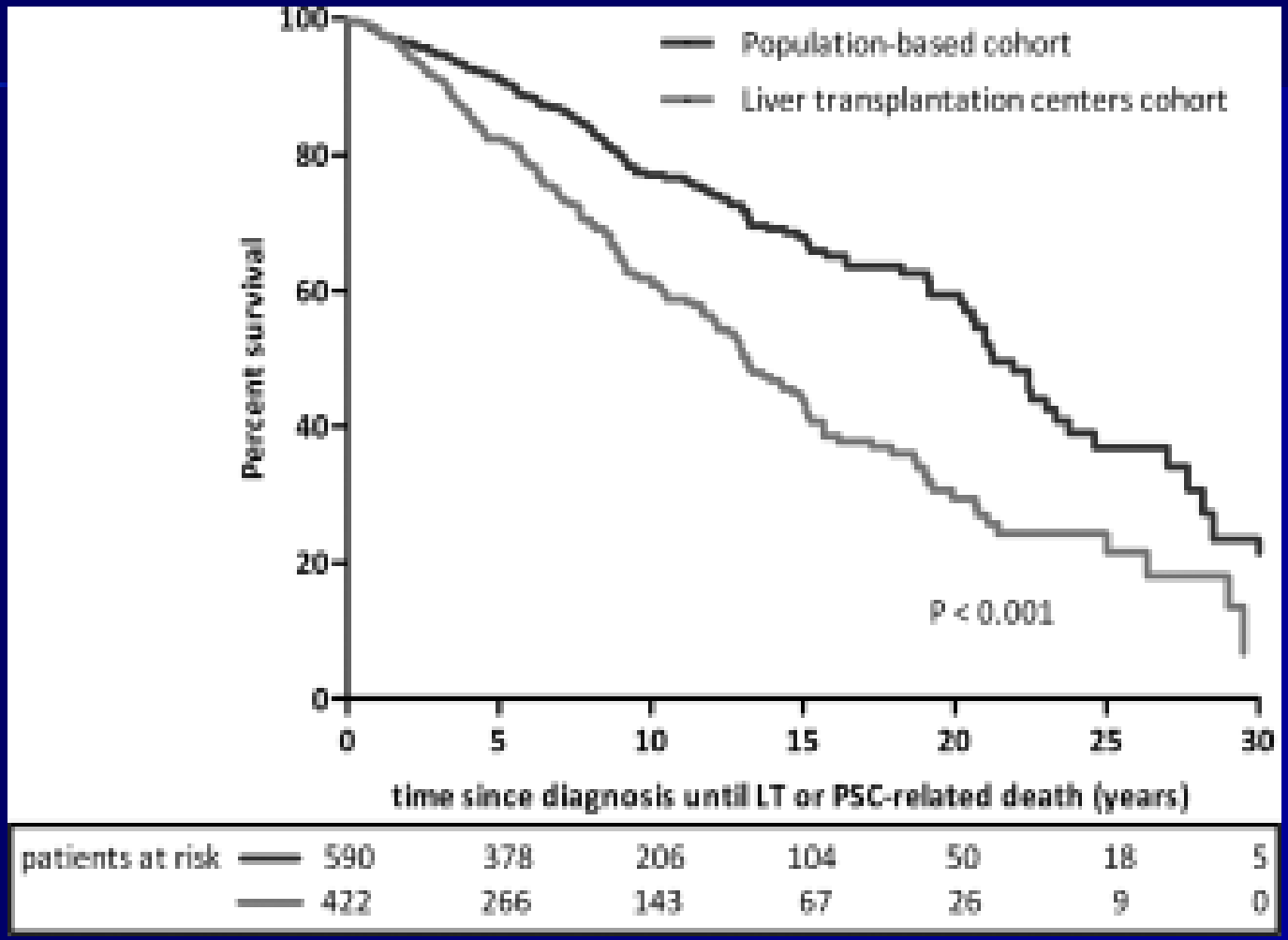


Natural History

- Progressive
- Highly variable course
- Spontaneous resolution does not occur
- Not improved by colectomy for UC
- Pts who are asymptomatic may have better survival

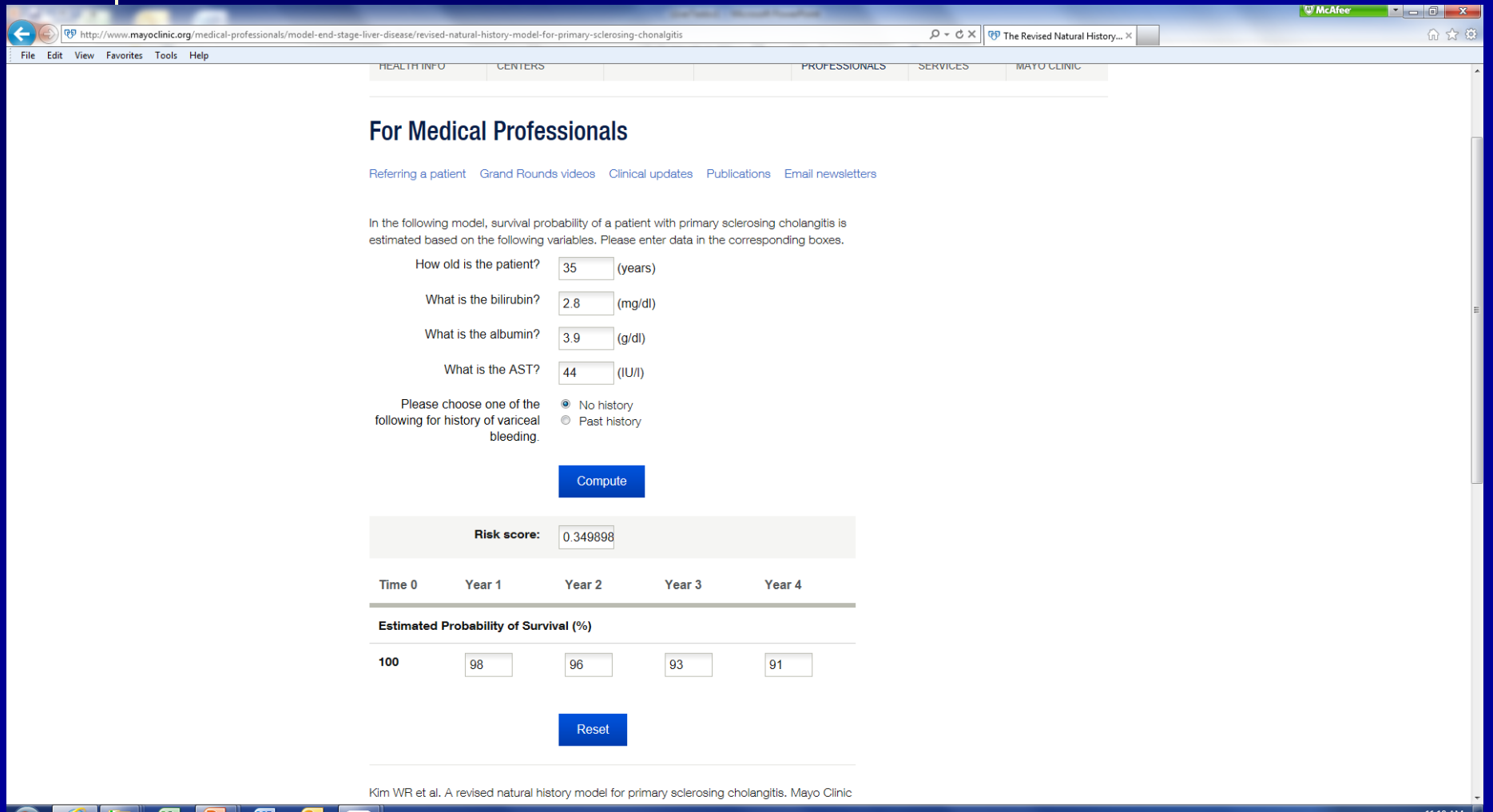


Hepatology 2006;44:747



Hepatology 2013;58:2045

Mayo Risk Score



http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/revised-natural-history-model-for-primary-sclerosing-chonalgitis

The Revised Natural History...

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In the following model, survival probability of a patient with primary sclerosing cholangitis is estimated based on the following variables. Please enter data in the corresponding boxes.

How old is the patient?	35	(years)
What is the bilirubin?	2.8	(mg/dl)
What is the albumin?	3.9	(g/dl)
What is the AST?	44	(IU/l)

Please choose one of the following for history of variceal bleeding.

- (•) No history
- ( ) Past history

Compute

Risk score: 0.349898

Time 0	Year 1	Year 2	Year 3	Year 4
Estimated Probability of Survival (%)				
100	98	96	93	91

Reset

Kim WR et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clinic

11:18 AM 3/7/2014

Disease related complications

- Infection
  - 33-50%
- Strictures
- Stones: gallbladder, bile duct
- Cirrhosis
  - May be present at time of diagnosis
  - Portal hypertension, varices, liver failure

Malignancy

- Bile duct cancer (cholangiocarcinoma)
  - Can occur at any time
  - 10-20% lifetime risk, 0.5-1%/year
- Colon cancer/dysplasia
- Pancreatic cancer
- Liver cancer (hepatocellular carcinoma)

Complications cont'd

- Bone disease
- Itching
- Hypercholesterolemia
- Fat soluble vitamin (A, D, E, K) deficiency
- Malabsorption
- Fatigue

Therapy

- Atypical autoimmune disease
- Responds poorly to typical immunosuppressive therapies

Therapy

- There is no proven effective medical treatment
- No therapies have been proven to prolong survival or change the natural history
- Therapy of IBD has little effect on PSC course and vice versa

- *Liver transplantation*

Therapy

- Most therapies are directed at the complications rather than the underlying cause of PSC

Medical Treatments

- Antibiotics for infections
- ERCP/PTC
  - Stones
  - Strictures
  - Bile Duct Cancers
- UDCA
  - Pros/cons
- Anti-pruritic agents

Medications

- Penicillamine
- Cyclosporine
- Methotrexate
- Pentoxifylline
- Azathioprine
- Colchicine
- Budesonide
- Prednisone
- Vancomycin
- MMF
- Pirfenidone (antifibrotic agent)
- Etanercept
- Nicotine
- Flagyl
- Minocycline
- Silymarin
- Tacrolimus
- Ursodeoxycholic acid

Ursodeoxycholic Acid (UDCA)

UDCA: Potential Benefits

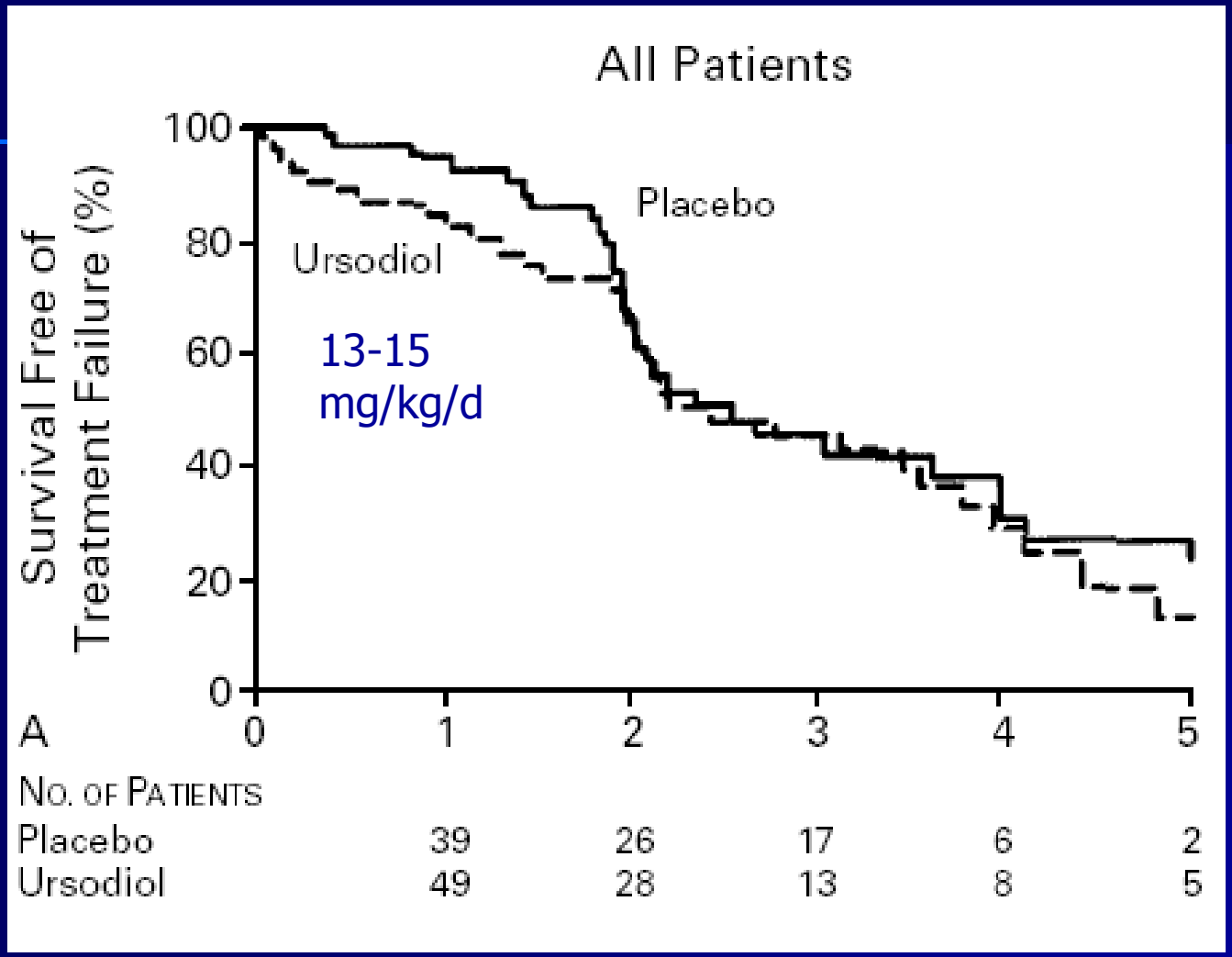
- Improves liver enzymes
- May improve portal inflammation and cholangiographic appearance
- Chemopreventative
- Safe and well tolerated
- Antioxidant
- Immune modulator
- Stabilizes biliary membranes

UDCA

- A beneficial effect of UDCA on SURVIVAL of pts with PSC has NOT been demonstrated
- Does NOT slow course or prolong survival
- Data on symptoms and QOL controversial
- Costs/benefits

UDCA for PSC: Mayo Clinic Trial

Death, LTx, biopsy, liver failure



Lindor KD. *N Engl J Med* 1997;336:719-21

Why use High Dose (17-30 mg/kg UDCA?

- Observed trends for LFT improvements
- Perhaps higher dose will show better results.
- Any survival benefit?

Table 4. Development of Primary Endpoints

Primary Endpoints	UDCA	Placebo
Death	5	3
Liver transplantation	11	5
Minimal listing criteria for liver transplantation	13	10
Development of cirrhosis	6	4
Esophageal and/or gastric varices	15	5
Cholangiocarcinoma	2	2
Total endpoints	52	29
Number of patients reaching a primary endpoint	30	19
Number of patients reaching death, orthotopic liver transplantation, minimal criteria listing	22	15

Lindor et al; Hepatology 2009 50 (3)808-814

- Adjusted HR 2.3 ($p<0.01$) for primary endpoint on UDCA
- Adjusted HR 2.1 ($p=0.038$) for death, transplantation or min. listing criteria.
- Serious A.E. (63% UDCA vs. 37% placebo, $p<0.01$)

Conclusions: HD URSO

- Based on the evidence:
  - Some LFT improvement
  - No significant symptom improvement
  - Based on survival outcomes and adverse events, no improvement - increased harm .

Bile Acids and Colorectal Cancer (CRC)

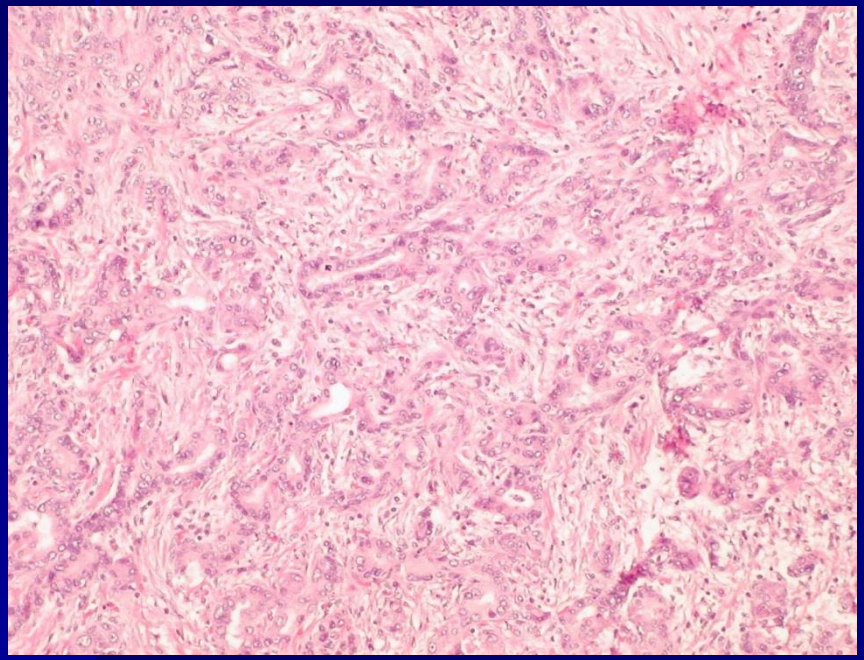
- Dysplasia in UC patients is associated with high fecal levels of bile acids
- CRC is associated with high fecal and serum levels of bile acids
- AASLD guidelines do NOT recommend

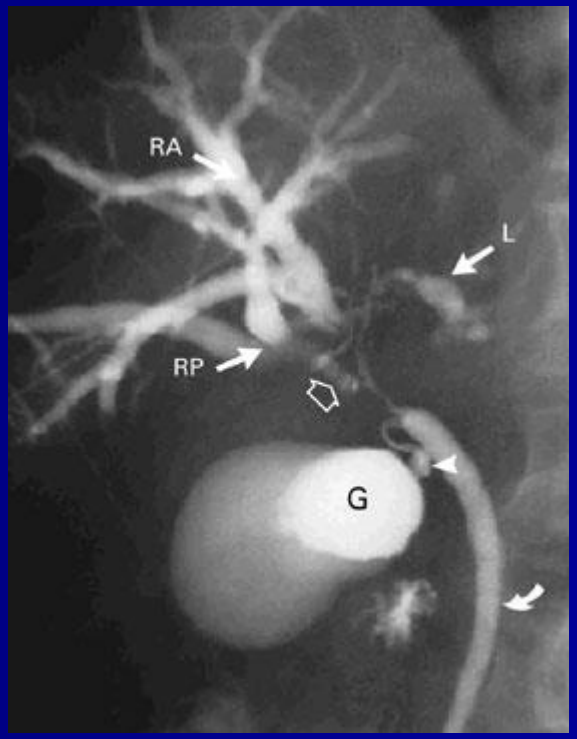
Cholangitis

Cholangitis

- Antibiotics
- ?role of prophylactic antibiotics
- Doesn't slow progression of PSC
- Stenting

Cholangiocarcinoma





Cholangiocarcinoma Management

- Screening ineffective
  - CA 19-9
  - Imaging
- Liver transplantation for selected few

Itching – simple treatments

- keep skin moist (esp. in Denver)
  - Neutrogeena (best, expensive)
- avoid narcotic pain pills
- topical (put directly on skin)
  - hydrocortisone cream
  - Sarna
  - citrus body lotion
  - Solarcaine spray/lotion
  - oatmeal bath
  - ice pack

Itching - treatments

- benadryl/atarax
  - often recommended, rarely helpful
- ursodeoxycholic acid (urso, actigall)
- cholestyramine (questran)
  - Tastes bad, stomach upset, drug binder
- Sertraline
- Rifampin
  - Interacts with some drugs, orange urine

Itching - treatments

- ativan, valium
  - only for short-term treatment
- Revia (naltrexone)
- phenobarbital

Itching - treatments

- other
  - tanning booth, phototherapy
  - hemodialysis with charcoal filter
  - ??

Bone Disease

- Osteopenia at diagnosis in 50%
- 1/3 develop pathologic fractures

- DEXA scans
- Calcium
- Estrogens
- ?bisphosphonates

Other

- Screen for fat-soluble vitamin deficiencies (A, D, E, K)
- Treat lipids
- Vaccination : HAV, HBV, influenza
- Work up diarrhea
- Annual colonoscopy if UC, o/w colonoscopy if no prior history of IBD

When is it time to consider Liver Transplantation?

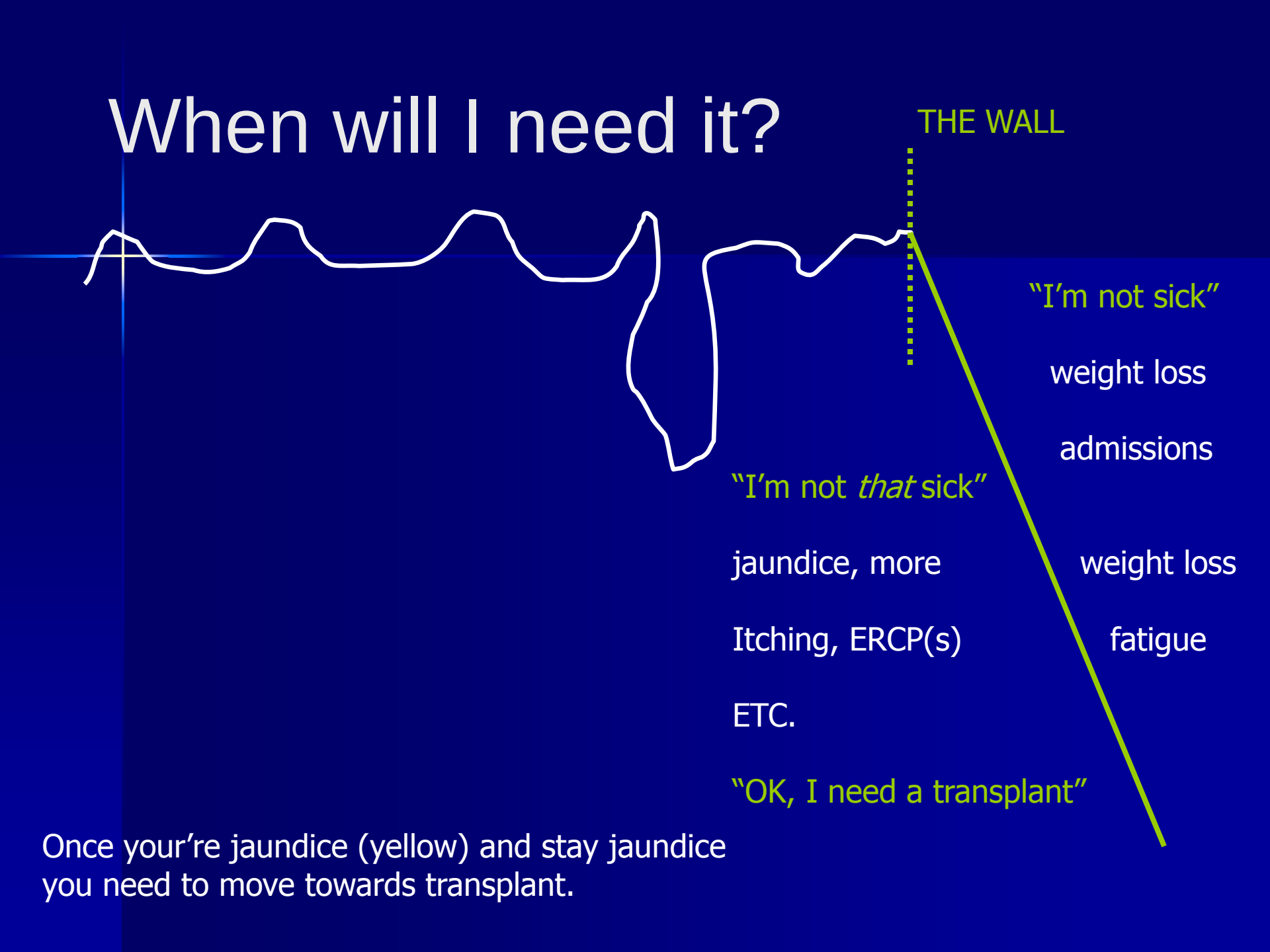
Questions about Transplant

- Will I need it?
- When will I need it?
- How will it happen?
- What happens afterwards?

Will I need it?

- About ½ our patients are transplanted 10 years after diagnosis
- …that means ½ are not transplanted

When will I need it?



Once your're jaundice (yellow) and stay jaundice you need to move towards transplant.

How will it happen?

- Deceased-donor transplant (full-size liver from a dead person)
- Living-donor transplant (1/2 liver from living donor)
- Off-shore transplant (China, India)

	deceased-donor	living donor
organ size	+++	+
timing	+	+++

"Is it better to wait indefinitely on a whole liver

or take ½ a liver with ideal timing?"

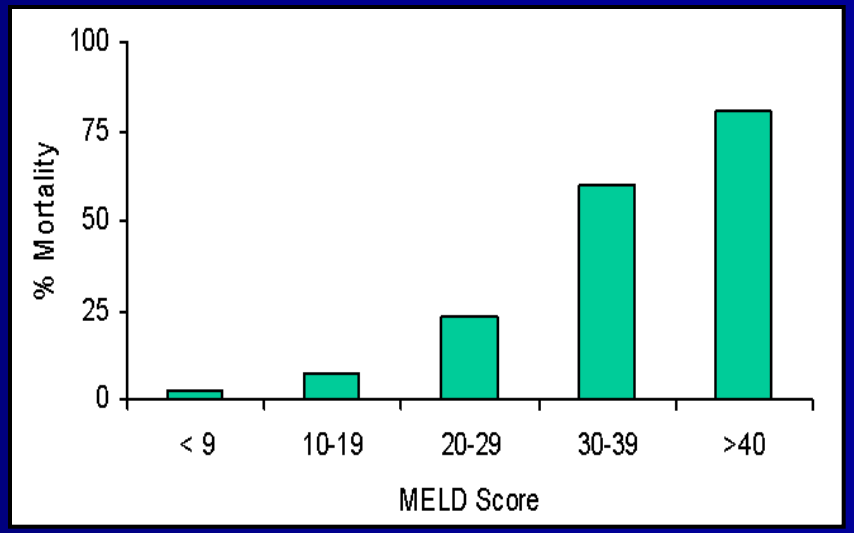
Model End Stage Liver Disease

MELD Score =

$0.378*\log_e(\text{bilirubin[mg/dL]}) +$

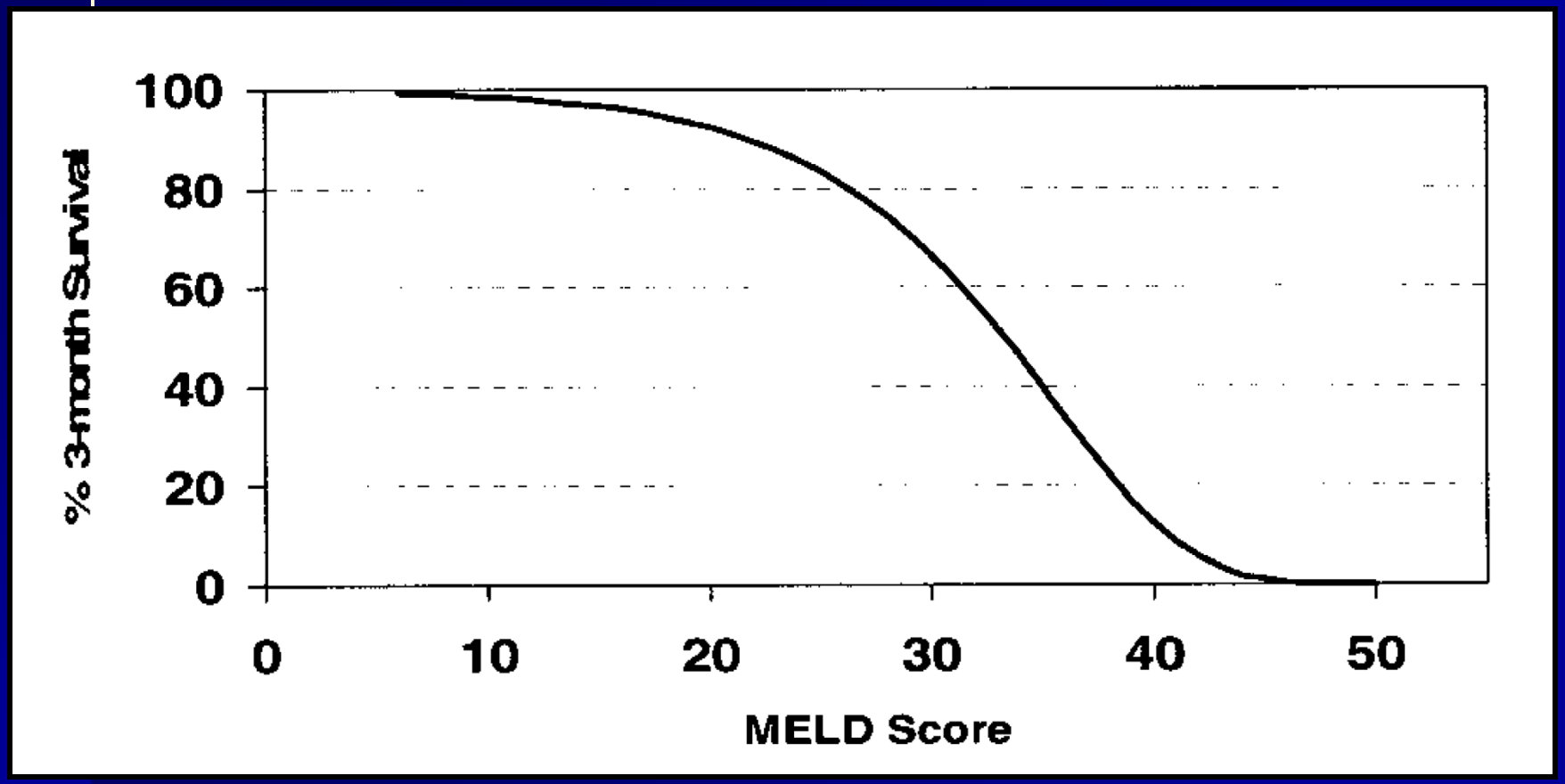
$1.120*\log_e(\text{INR}) +$

$0.957*\log_e(\text{creatinine [mg/dL]}) + 0.643$



Wiesner et al. *Gastroenterology* 2003;124:91-6

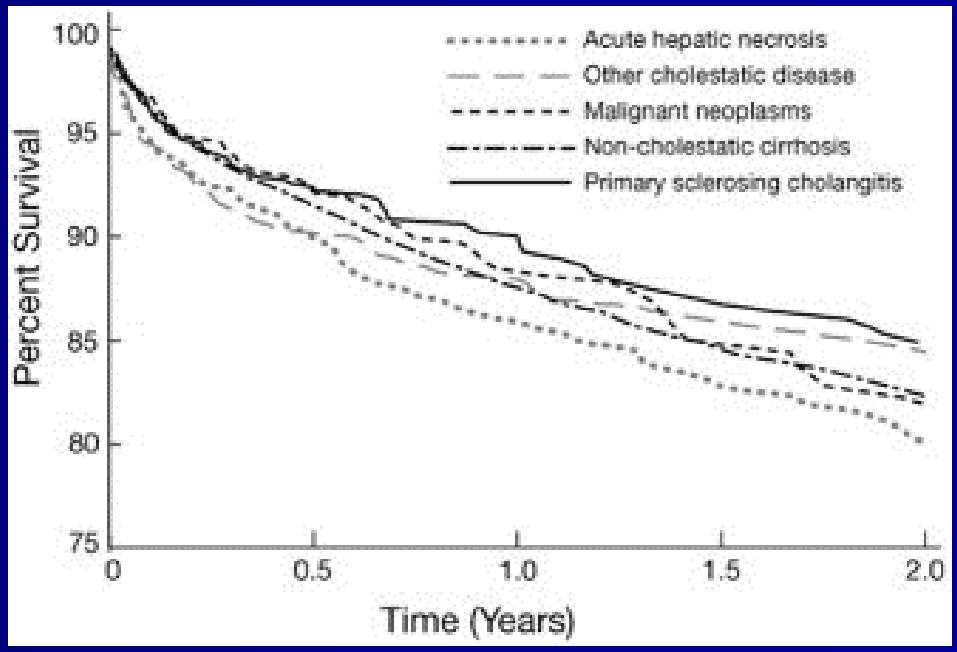
Estimated 3-Month Survival Based on Listing MELD in Patients on the Waiting List



Wiesner et al. *Gastroenterology* 2003;124;9:91-6

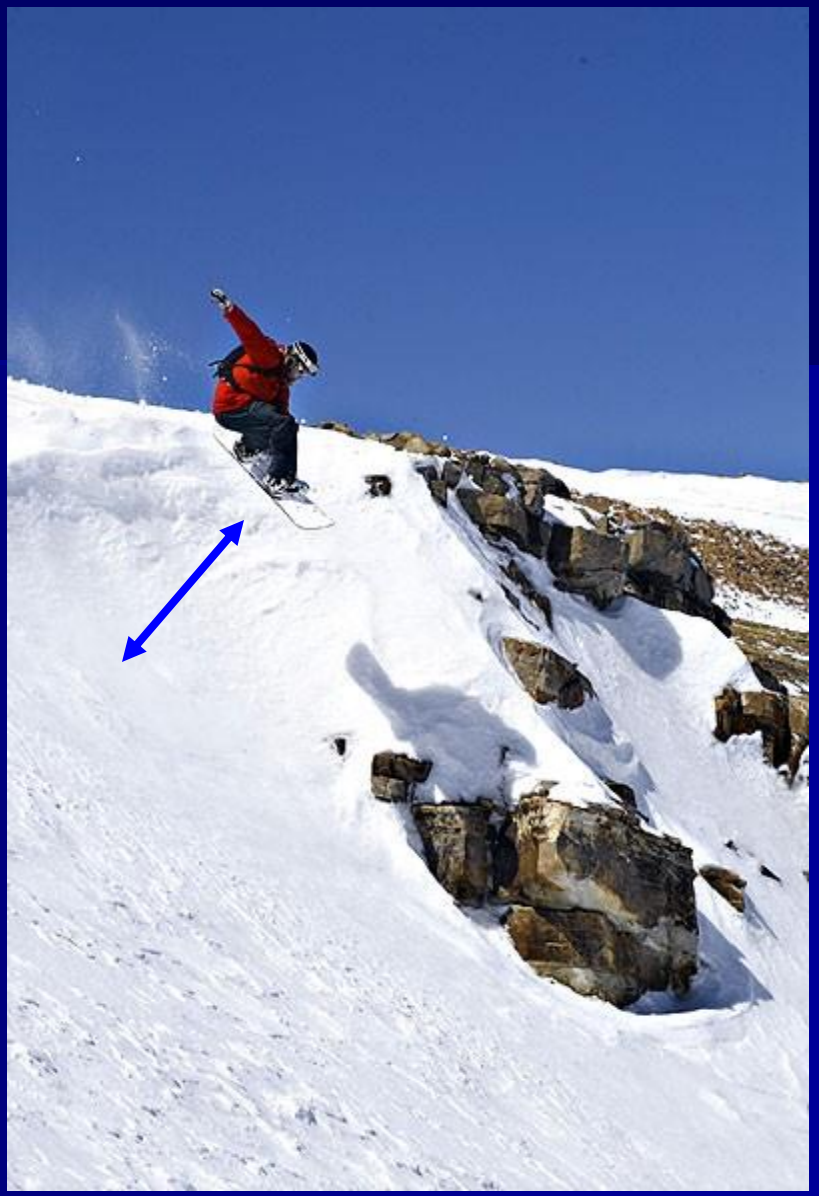
What will happen afterwards?

- 90% 1 year survival
- 84% 2 years
- Retransplantation rates higher PSC
- 20-30% recurrence PSC
  - Most do well
  - r/o other causes



Inflammatory Bowel Disease Course

- Course variable
- *De novo* IBD may occur
- More research needed
- Transplantation does not affect incidence of CRC



Conclusions

- PSC is a chronic immune mediated disease with unclear etiology
- Medical therapy limited
- Currently targeted at complications
- Progressive biliary and liver damage can lead to portal hypertension and liver failure over 10-15 years from diagnosis

Conclusions

- Early referral to transplant center
- Liver Transplantation only treatment for advanced disease
- Excellent outcomes
- New therapies needed
  - LOXYL2 inhibitor (simtuzumab)
- Support Systems