Primary Sclerosing Cholangitis

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Definition

- Chronic, cholestatic liver disease of unknown etiology characterized by diffuse inflammatory destruction of intrahepatic and/or extrahepatic bile ducts that results in bile stasis, hepatic fibrosis, cirrhosis, and end-stage liver disease

Primary Sclerosing Cholangitis

- Fourth decade of life
- 1.25 per 100,000 men and 0.54 per 100,000 women per year
- 20.9 and 6.3 per 100,000 men and women
- Median survival between 12 and 18yrs
- Smoking :Protective
- M : F 2 : 1
- Cholangiocarcinoma prevalence 6-20%

  Incidence 1-5% / year

Martin et al *Ann Surg* 1990, Ponsioen et al *Gut* 2002, Boberg et al *Scand J Gastro* 2002

IBD and PSC

2-10% of IBD patients will develop PSC

~ 70% of PSC patients have evidence of IBD

Chronic ulcerative colitis
Crohn disease
Chronic pancreatitis
Sicca syndrome
Hypereosinophilia
Reidel thyroiditis
Celiac disease
Autoimmune hemolytic anemia
Sarcoidosis
Glomerulonephritis
Autoimmune Hepatitis

Pathogenesis of PSC

- Multifactorial/ Complex
- Cellular immunity
- Autoimmunity?
- Bacterial Antigens
- Aberrant Lymphocyte Homing
- Cytokines

AETIOLOGY OF PSC?

HLA polymorphisms

PSC A1, B8, DR3, DQ2

HLA haplotypes and primary sclerosing cholangitis

HLA haplotypes **negatively** associated with PSC	HLA haplotypes associated with PSC	HLA haplotypes with **strong** association with PSC
DRB1*04-DQA1*03-DQB1*0302	DRB1*03-DQA1*0501-DQB1*02 DRB1*13-DQA1*0103- DQB1*0603 DRB1*15-DQA1*0102-DQB1*0602 Cw*0701-B8-DRB1*0301 B8-MICA5.1-MICB24-DR3	DRB1*03-DQA1*0501-DQB1*02

AETIOLOGY OF PSC?

Other gene polymorphism

- CTLA-4
- CCR5
- IL-1
- IL10
- MMP-3

DR2 associated with younger onset

DR4 associated with rapid disease progression

Donaldson *Hepatol* 1991, Mehal *Gastro* 1994

AETIOLOGY OF PSC?

Autoimmunity

- 2:1 M:F ratio and poor response to immunosupression imply PSC is not a classical autoimmune disease

- PSC is associated with the “autoimmune” haplotype

- 25% of PSC patients have ≥ 1 autoimmune disease

  c.f. 4% of IBD Saarinen *Am J Gastro* 2000

AETIOLOGY OF PSC?

Autoantibodies

Antibody	Prevalence
Anti-nuclear antibody (ANA)	7–77%
Anti-smooth muscle antibody (ASMA)	13–20%
Anti-endothelial cell antibody (AECA)	35%
Anti-cardiolipin antibody	4–66% Thyroperoxidase 7–16%
Thyroglobulin	4%
Rheumatoid factor	15%

NB: note antimitochondrial antibody is only rarely detected in PSC (-10%). This is useful in differentiating PSC from PBC

AETIOLOGY OF PSC?

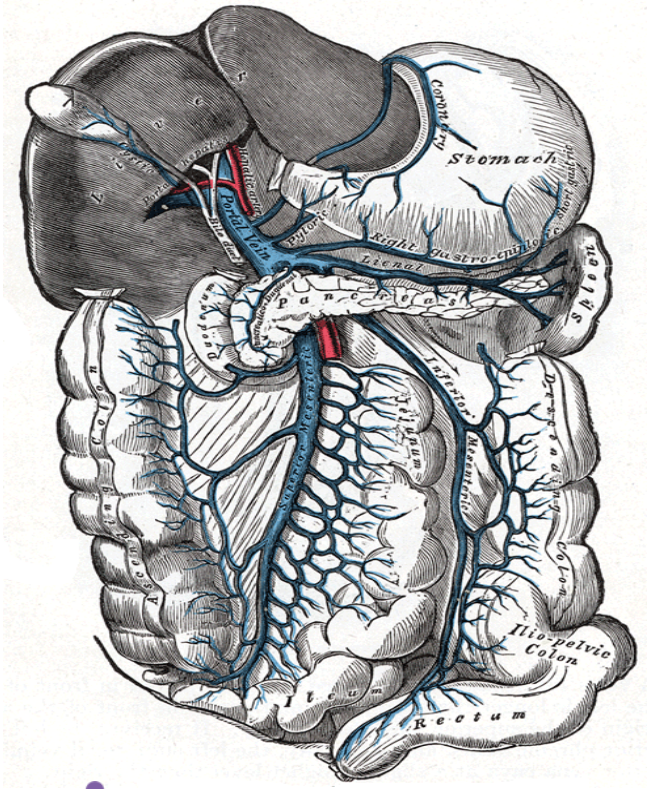
- To date there is no convincing model of the pathogenesis of PSC that implicates Anti-Neutrophil Ab's

  Atypical p-ANCA (p-ANNA)

- Monoclonal Ab to colonic epithelial protein in UC can cross react with biliary epithelial cells in patients with PSC and UC- ? Common antigen Mandal et al *Gastro* 1994

AETIOLOGY OF PSC?

Bacterial Antigens



Investigation confounded by contamination of bile duct at ERCP

Rats develop hepatic injury similar to PSC after artificially induced SBBO

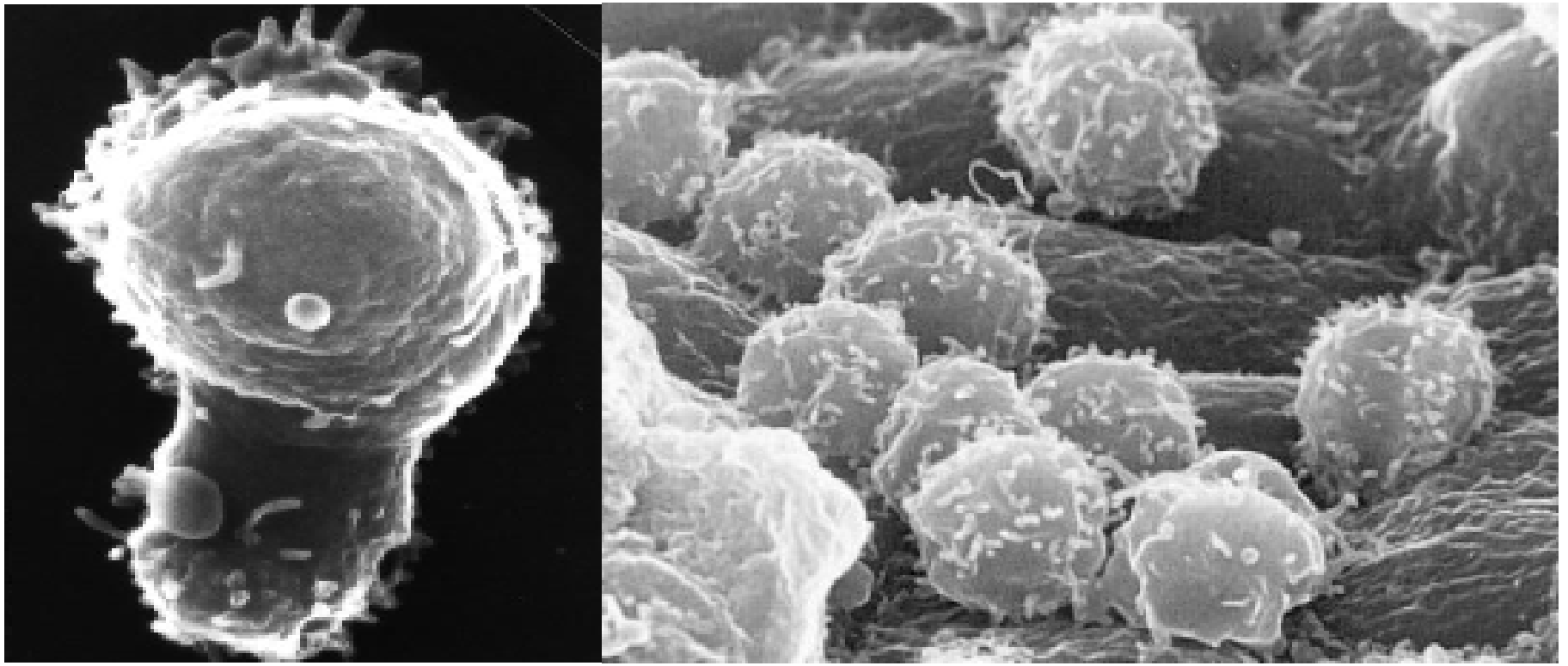
Lichtman et al *Gasto* 1990

Bacterial peptides instilled rectally in rats with a chemical colitis appear quickly in bile and Initiate small duct cholangitis

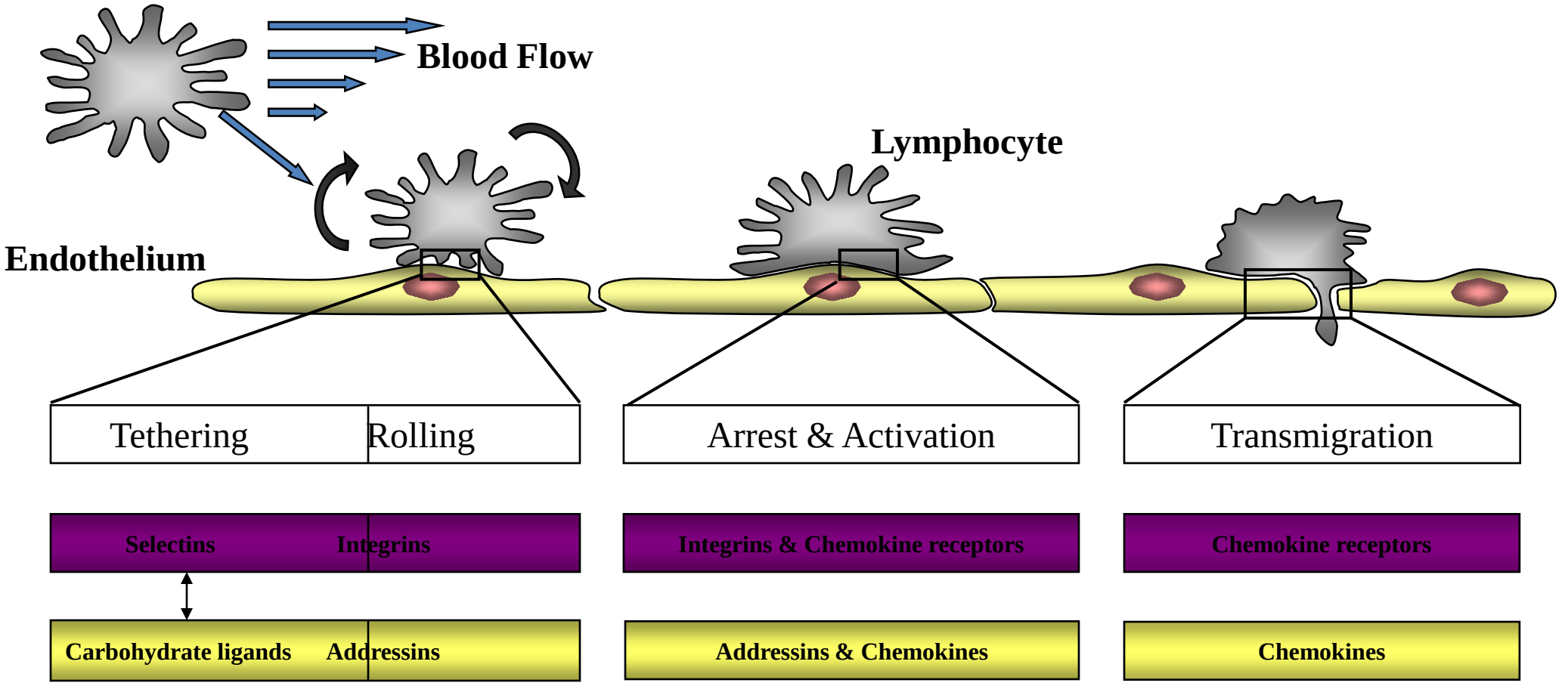
Yamada et al *J Gastro* 1994

AETIOLOGY OF PSC?

Aberrant Lymphocyte Homing

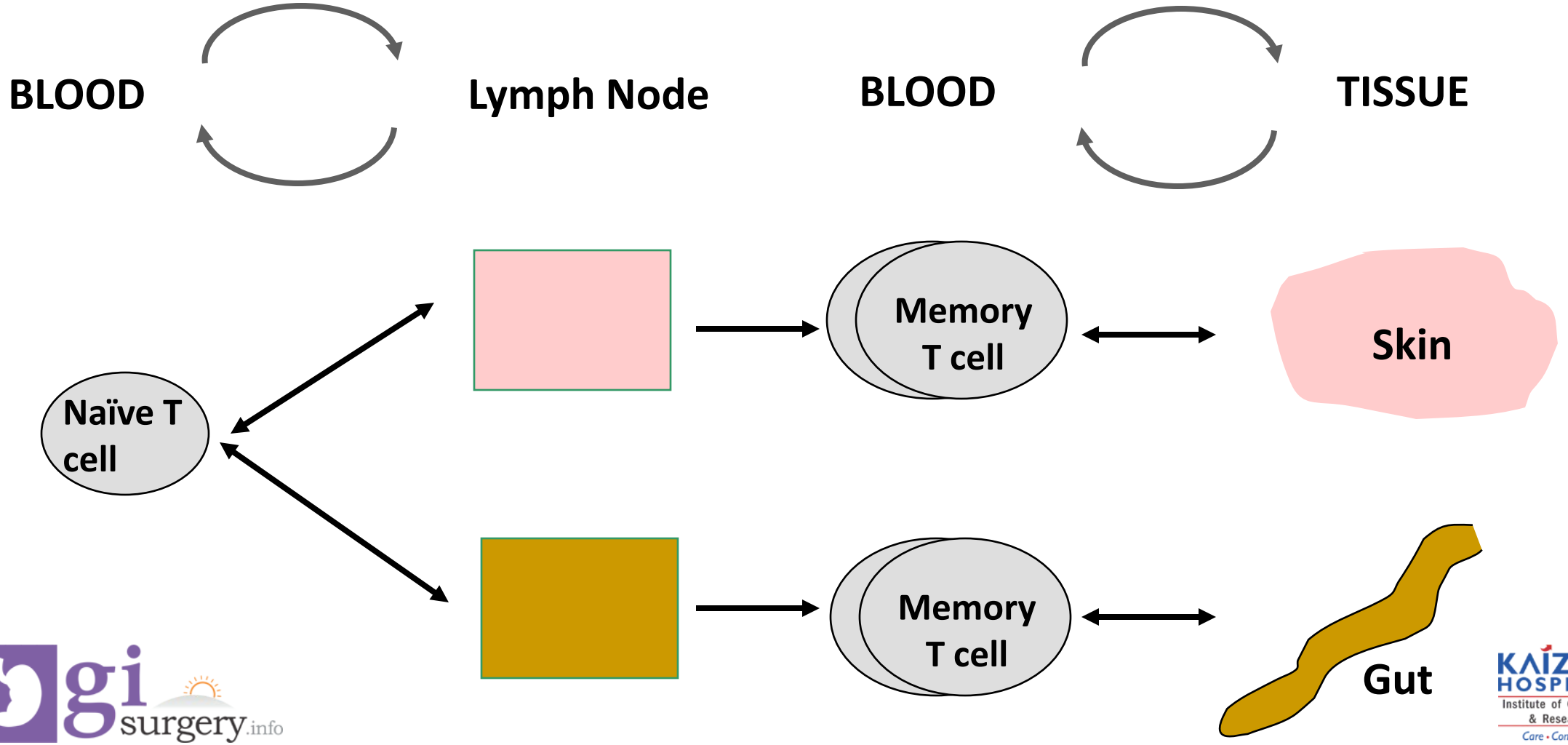


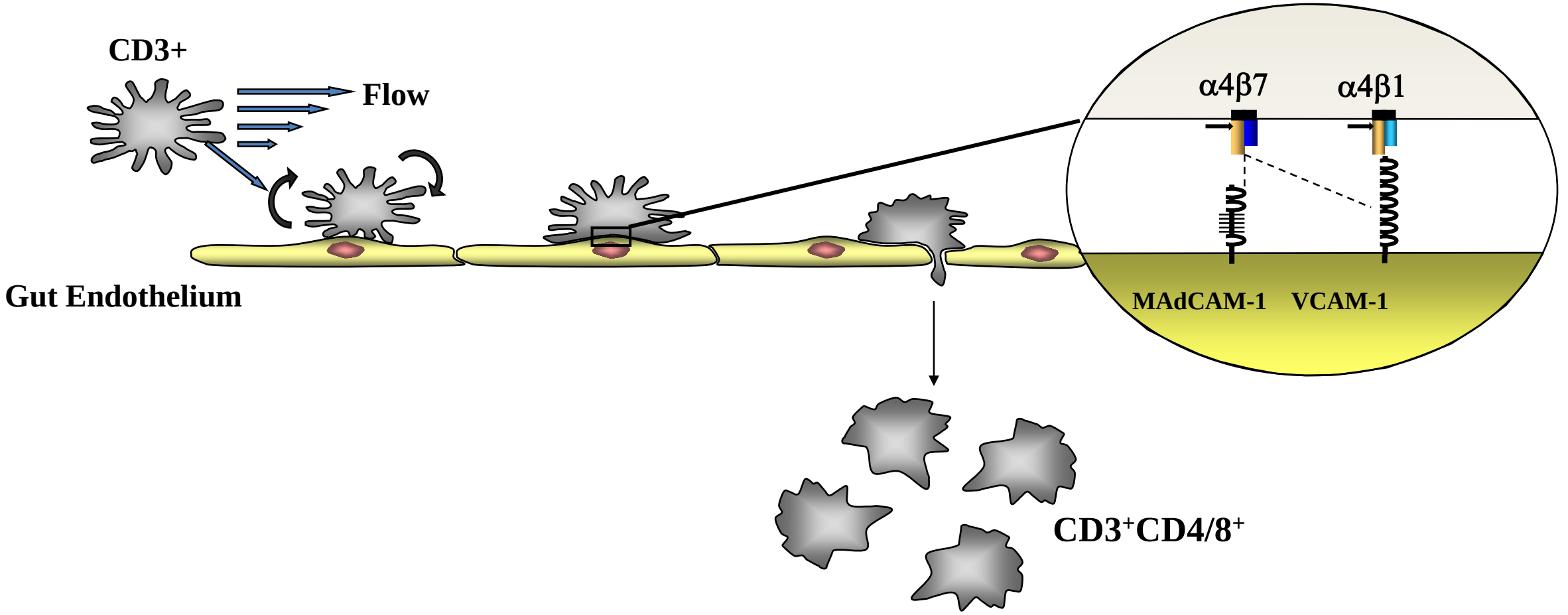
Adhesion cascade



TISSUE SPECIFIC HOMING OF MEMORY EFFECTOR T LYMPHOCYTES

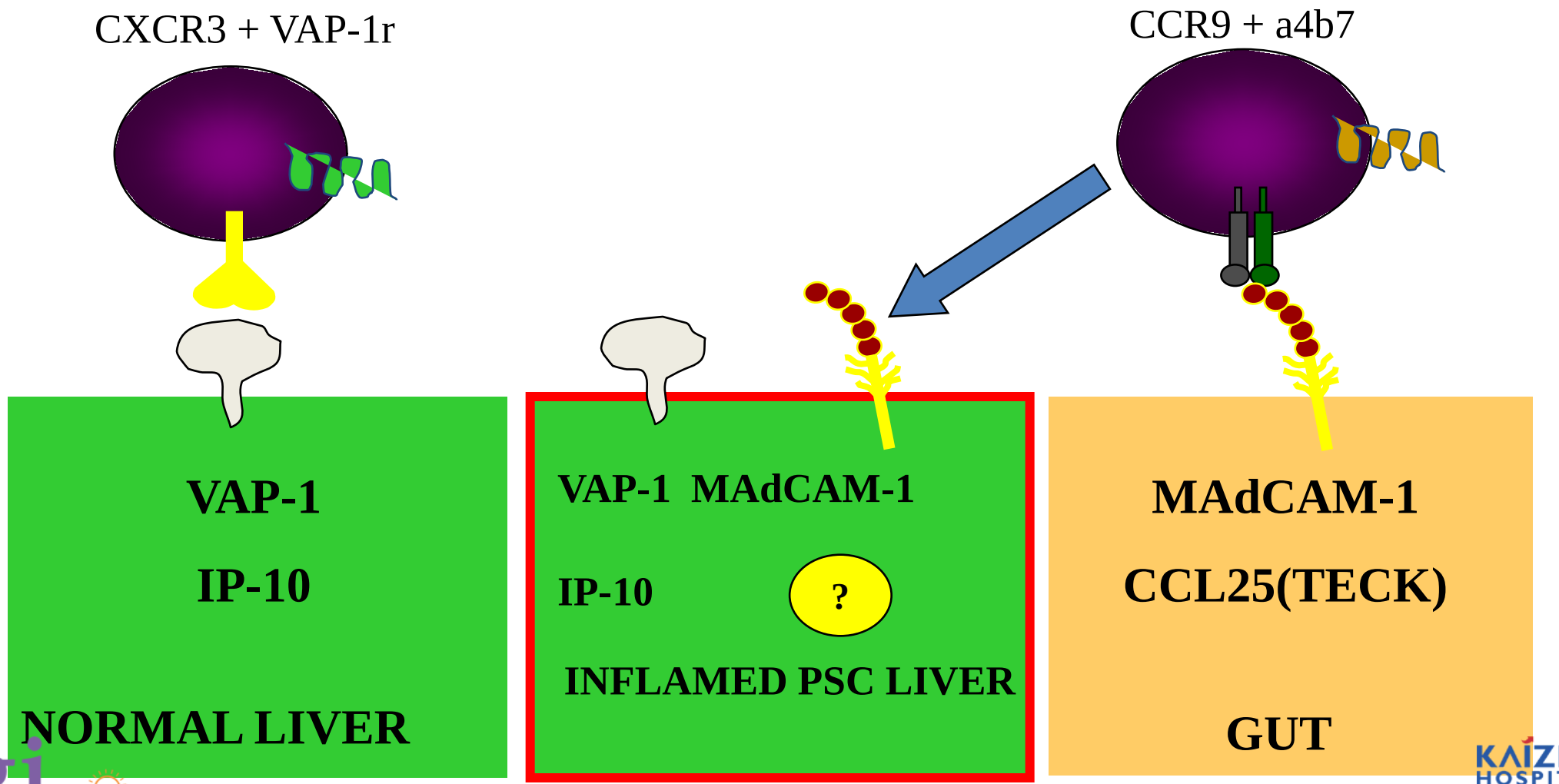
I Weissman, E Butcher, C Mackay, S Shaw and S Jalkanen





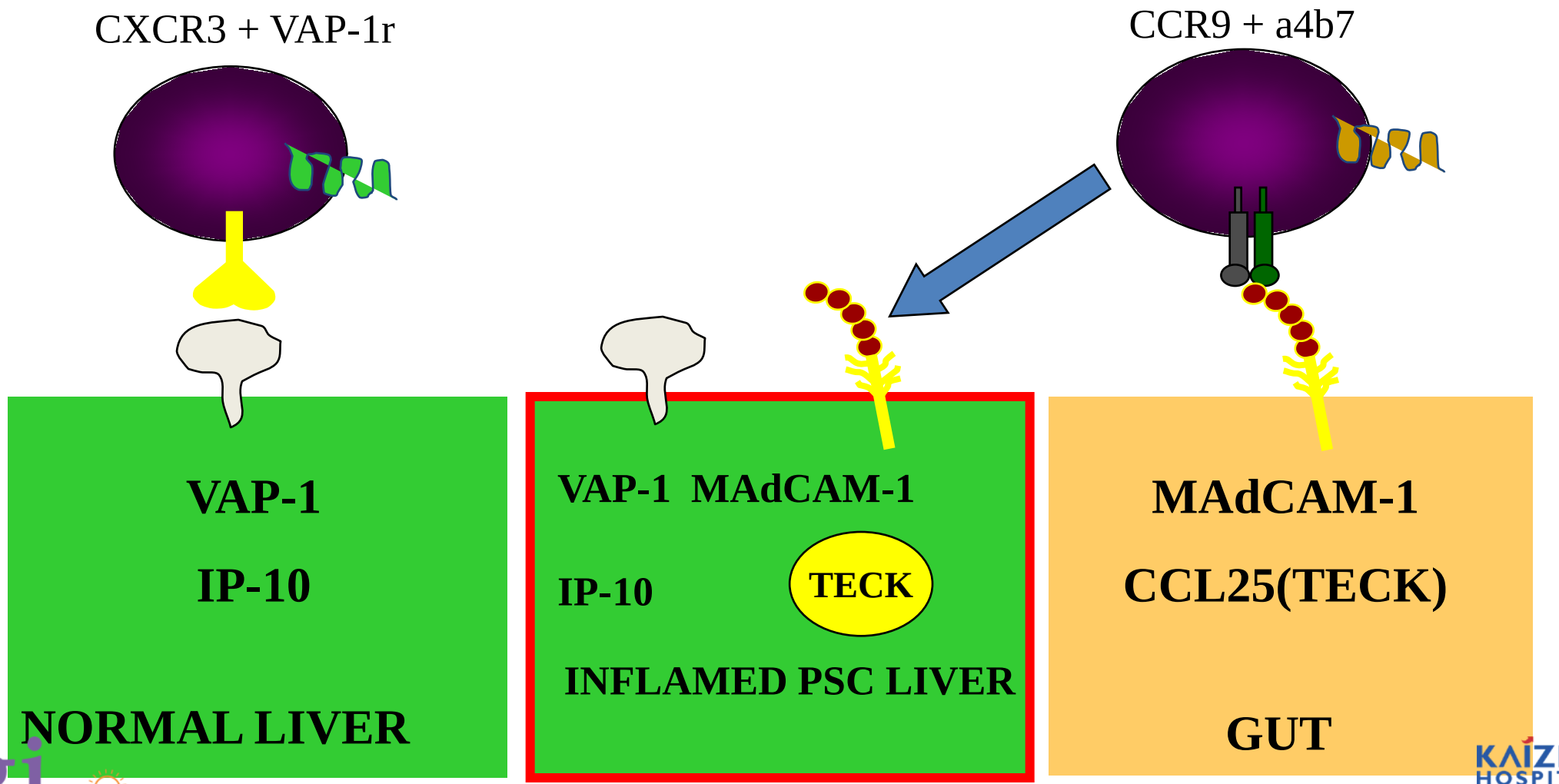
Tissue specific T cell recruitment

Grant AJ *Lancet* 2002



Tissue specific T cell recruitment

Grant AJ *Lancet* 2002, Eksteen B, Grant AJ et al *JEM* 2004, Eksteen B, Adams DH *Nat Rev Immunol* 2006



Clinical Features

- Depending on the disease stage
- 15% to 40% of patients are asymptomatic
- Cholestatic liver disease or hepatic failure
- Abdominal pain (20%), pruritus (10%), diarrhea (8%), jaundice (6%), fatigue (6%), and fever (4%)

- Symptoms of bacterial cholangitis
- Jaundice, hepatomegaly, splenomegaly, and excoriations
- Biliary cirrhosis and portal hypertension

Diagnosis of PSC

- Most diagnoses are made after the discovery of abnormal LFT's at IBD FU
- Cholestatic LFT's (normal or fluctuating)
- Atypical p-ANCA -in 33-88%
- Abnormal MRCP or ERCP
- Liver Biopsy

- Clinical presentation, biochemical profile, and characteristic cholangiographic appearance of the bile ducts

- 1) absence of previous operative trauma to the biliary system;
- 2) sclerosis and stenosis involving all or most of the extrahepatic bile ducts
- 3) exclusion of malignant disease involving the biliary tree, such as cholangiocarcinoma
- 4) absence of calculi in the gallbladder and common bile duct

- 1) Characteristic cholangiographic abnormalities of the biliary tree
- 2) Compatible clinical and biochemical findings, typically of ductal cholestasis with elevated serum alkaline phosphatase level for at least 6 months duration
- 3) Exclusion of other causes of secondary sclerosing cholangitis (ssc).

Causes of Secondary Biliary Cirrhosis
AIDS-associated cholangiopathy
Amyloidosis
Bile duct neoplasm (in the absence of primary sclerosing cholangitis)
Chemicals/drugs (e.g., 5-fluorouracil)
Choledocholithiasis
Congenital bile duct abnormalities (Caroli disease)
Iatrogenic biliary strictures/trauma
Recurrent pyogenic cholangitis
Autoimmune pancreatitis
Intraarterial chemotherapy
Abdominal trauma, surgical or blunt
Eosinophilic or mast cell cholangitis

Biochemical Studies

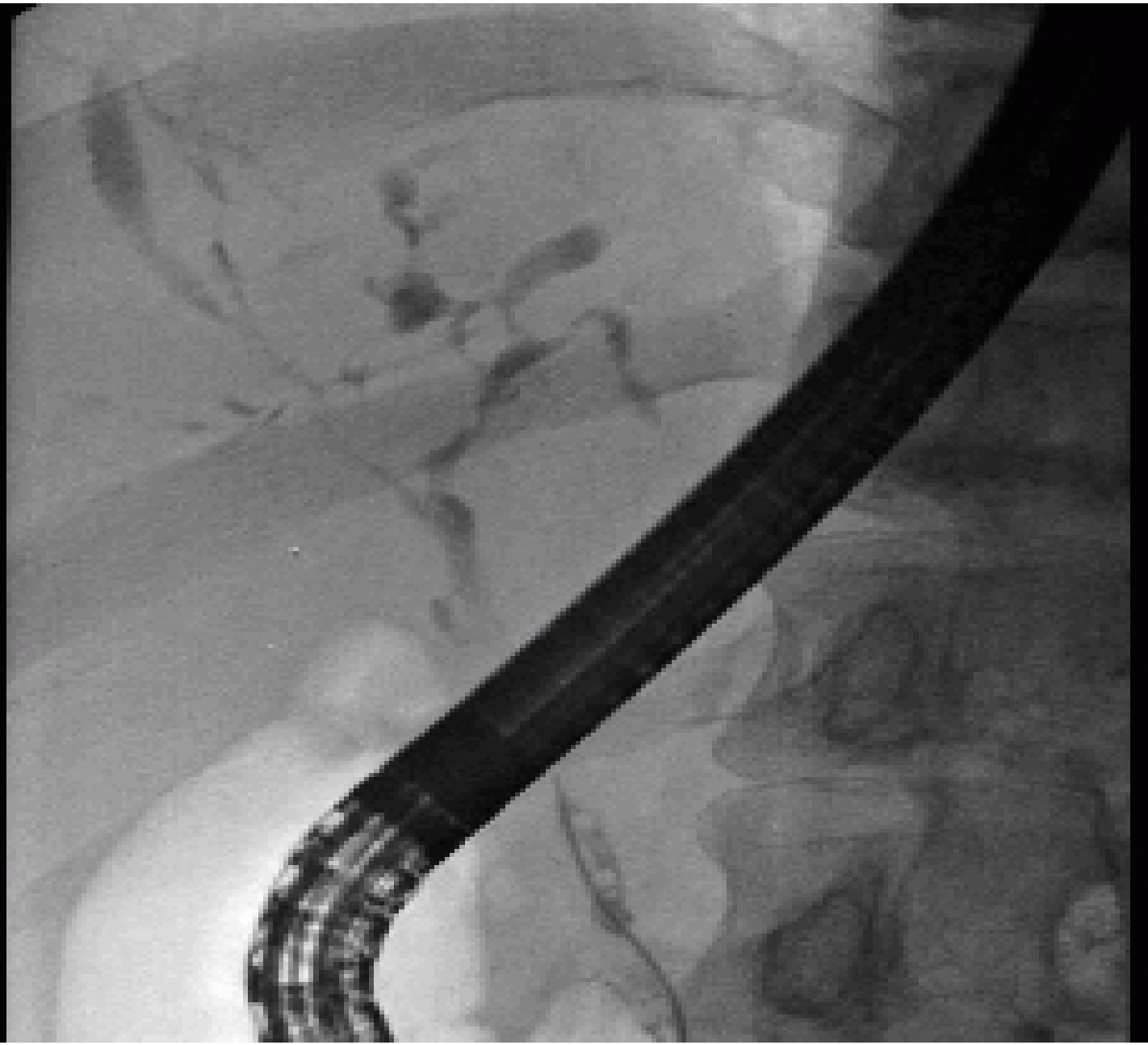
- Biochemical cholestasis of at least 6 months' duration gives reason to suspect PSC
- Alkaline Phosphatase
- Aminotransferases
- S.Bilirubin
- Hepatic Copper Level
- Autoantibodies Level

Imaging Studies

- ERCP is the gold standard
- Multifocal stricturing and beading throughout the biliary tree characteristic of alternating fibrosis and ectasia of the bile ducts
- Both the intrahepatic and extrahepatic biliary tree
- Diverticula
- Mural irregularities that produce a shaggy appearance

- Extent and distribution of disease
- Identifies benign dominant strictures for endoscopic dilation or stenting
- Allows brushings for cytology studies to screen for cholangiocarcinoma

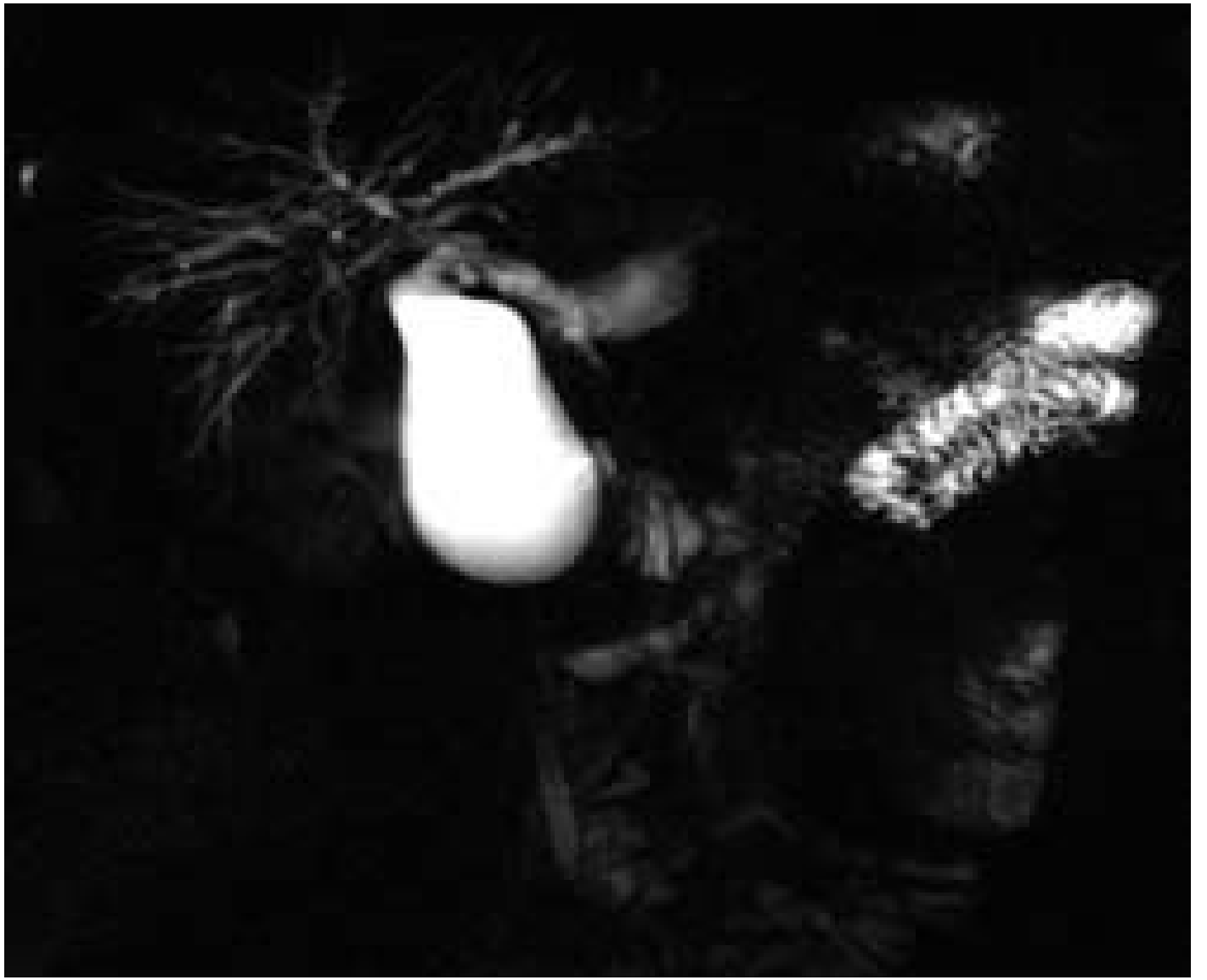
- Markedly dilated biliary ducts or ductal segments
- Presence of a polypoid mass of 1 cm or greater in diameter
- Progressive stricture formation



MRCP

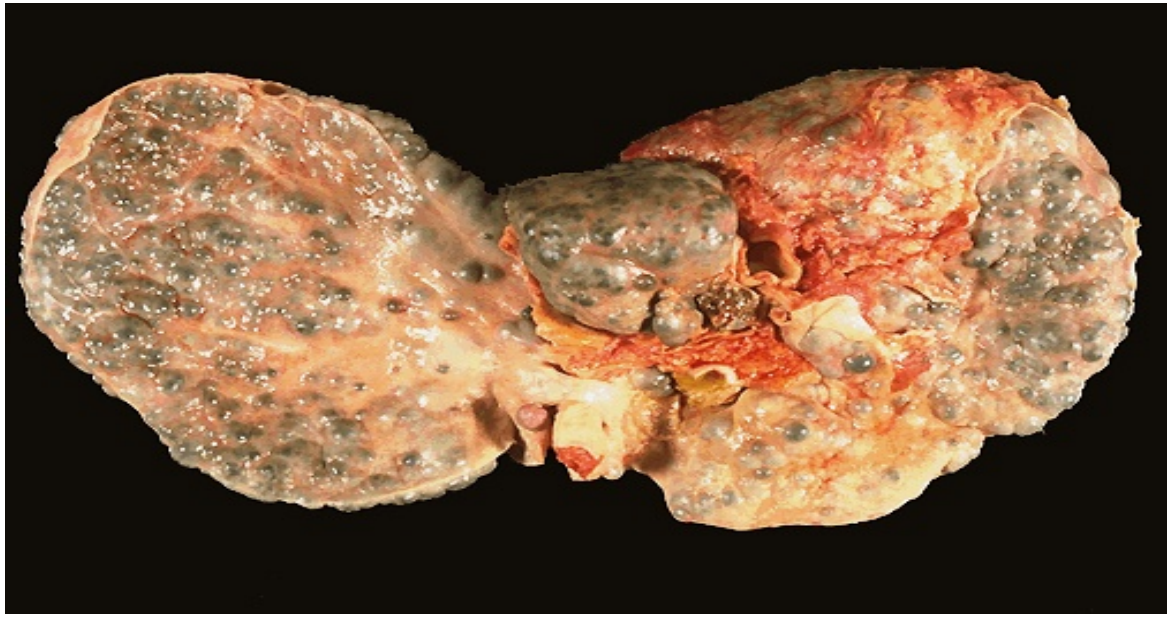
- 10% complication rate with ERCP
- Sensitivity and specificity - 80% to 82% and 87% to 98%

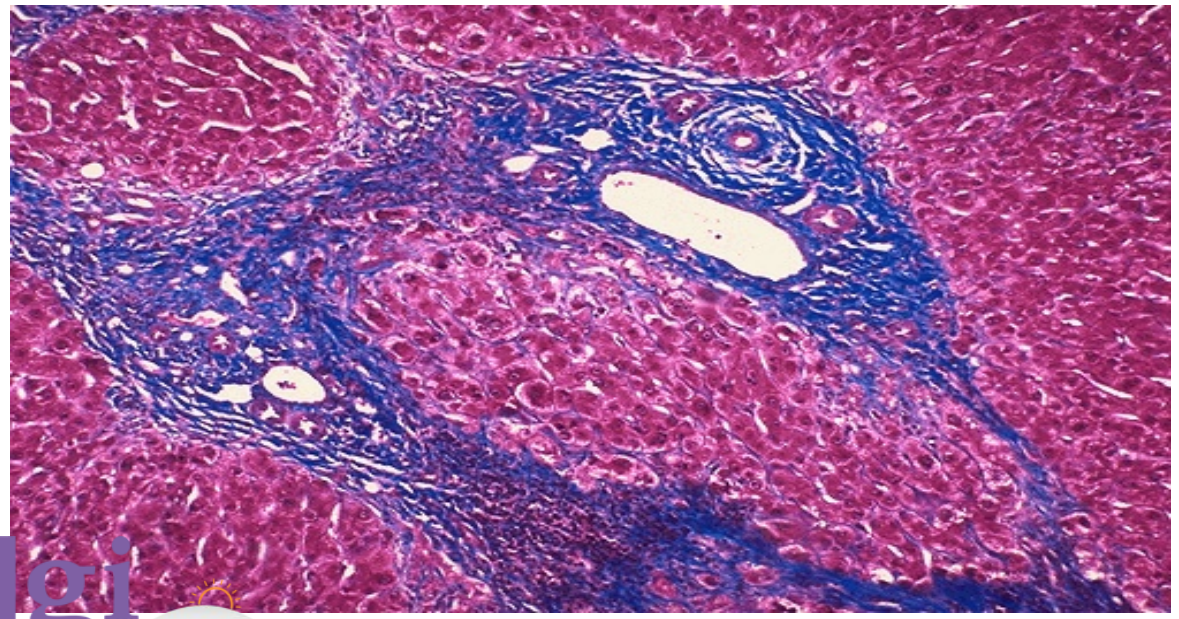
- MRC will likely replace diagnostic ERCP, but at present it is less sensitive and does not allow for biliary biopsy and cytology or therapeutic intervention.



Liver Biopsy

- The role of liver biopsy in PSC is to
- 1) exclude other causes of liver disease
- 2) diagnose small-duct PSC (discussed later)
- 3) define the disease stage for determining prognosis and assessing efficacy of treatment prior to entering in therapeutic trials.





Expanded portal tracts (Blue)

Onion skin appearance

1)PBC

2)Mechanical obstruction of larger bile ducts

3)Ductopenic rejection following liver transplantation

4) After intraarterial infusion of 5-fluorouracil

Ludwig's grading

Portal stage (stage I)	Portal edema, inflammation, ductal proliferation; abnormalities do not extend beyond the limiting plate
Periportal stage (stage II)	Periportal fibrosis and inflammation with or without ductal proliferation; piecemeal necrosis may be present
Septal stage (stage III)	Septal fibrosis or bridging necrosis can be identified
Cirrhotic stage (stage IV)	Biliary cirrhosis evident

Differential Diagnosis

Primary biliary cirrhosis
Drug-induced cholestasis
Congenital abnormality of the biliary tract
Idiopathic adult ductopenia
Cholestasis associated with autoimmune hepatitis or alcoholic liver disease
Bile duct carcinoma (cholangiocarcinoma)
Extrahepatic obstruction
Secondary sclerosing cholangitis

Small Duct PSC

- Subgroup of PSC
- Normal ERCP/MRCP
- Typical histological changes
- Benign course- only 12 % progress to classical PSC
- No reports of CholangioCa
- Similar rates of IBD (? CD>UC)

- **Specific complications related to PSC**
- Cholelithiasis
- Choledocholithiasis
- Dominant biliary strictures with or without recurrent bacterial cholangitis
- Cholangiocarcinoma
- Peristomal varices in patients who have undergone proctocolectomy and ileostomy for CUC.

- **Nonspecific psc complications are related to chronic cholestasis**
- Pruritus
- Steatorrhea
- Fat-soluble vitamin deficiency,
- Hepatic osteodystrophy
- **Complications associated with end-stage liver disease such as cirrhosis and portal hypertension.**

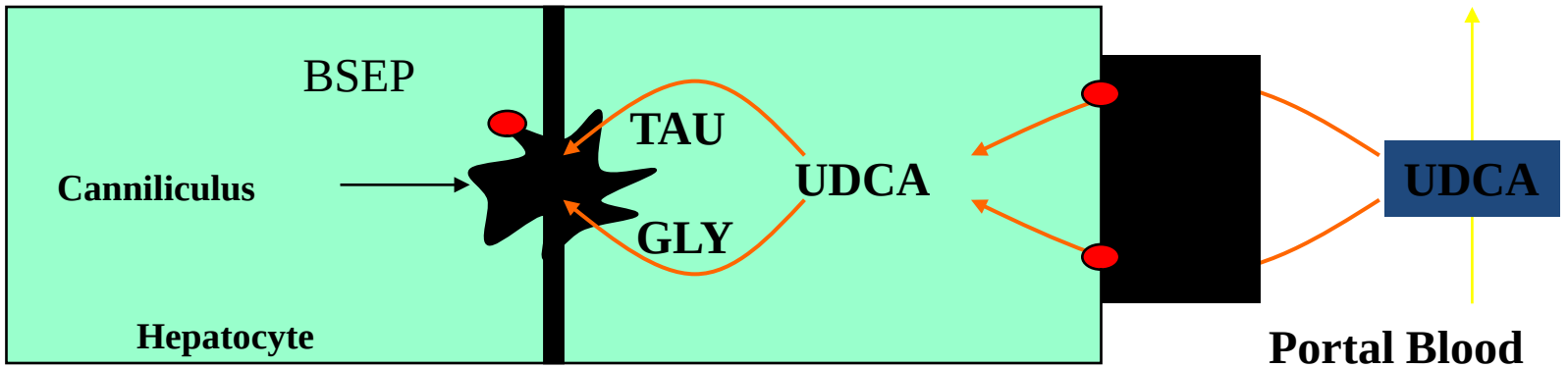
UDCA in PSC

- Widely used in cholestatic liver disease
- Hydophilic
- Mechanisms of action unclear

- Hydrophobic bile acids are toxic
- Probably not a detergent effect
- May cause damage by Fas-mediated apoptosis

UDCA – Mechanism's of Action

- Displaces hydrophobic bile acids
- Choleretic effect
- Small amounts normally present
- 80% absorbed through small bowel
- Reduced bioavailability in cholestasis



UDCA – Mechanism's of Action

Target	Mechanisms	Effects
Cholesterol	Intestinal absorption ↓	Biliary cholesterol decreased by 40-60%
	Conversion to bile acids ↑	Serum LDL and HDL cholesterol decreased
Bile acid pool	Ileal absorption of endogenous hydrophobic bile acids ↓	Serum UDCA increased by 10-64% Total bile acids ↑ Hydrophobic bile acids ↓ Unchanged hydrophilic bile acid pool
Bile flow	Exocytocis and canalicular transport ↑ (due to ↑ cytoplasmatic free Ca^{2+})	
	Modulation of membrane transport proteins Hypercholeresis	Excretory rates and bile acids transit time ↑
Gallbladder	Modulation of smooth muscle contractility (CCK receptor + cholinergic nerves)	Fasting gallbladder volume ↑ Postprandial gallbladder emptying ⇔
Gallbladder bile	Biliary total proteins ↓ Concanavalin A-binding fraction ↓	Crystallization-promoting activity ↓ Inhibition of cholesterol crystallization
Immune system	Expression of MHC class I and II ↓	Immunomodulatory effect T-cell hepatocellular damage ↓
Cells	Hydrophobic bile acid induced cell damage ↓ Apoptosis or necrosis ↓	Cytoprotection (e.g. liver damage ↓)
Neoplasms	Unknown (decreased fecal hydrophobic deoxycholate, lithocholate)	Chemo protection (neoplasm proliferation ↓)

↓, decreased; ↑, increased; ⇔, unchanged; MHC, major histocompatibility complex.

Trials of UDCA in PSC

- Limited good quality trials
- Small numbers
- Short follow up

Summary of trials of UDCA in PSC

Table 1. Trials of ursodeoxycholic acid (UDCA) in primary sclerosing cholangitis (PSC)

Author	Year	Number of patients	Dose of UDCA/day (mg/kg)	Type of trial	Trial period (months)	LFTs improved?	Symptoms improved?	Liver histology improved?
O'Brien *et al.*[182]	1991	12	10	Open-label	30	Y	Y	Not done
Beuers *et al.*[58]	1992	6	13–15	Double-blind placebo controlled	12	Y	N	Y
Lo *et al.*[183]	1992	23	10	Double-blind placebo controlled	24	Y	N	N
Stiehl *et al.*[59]	1994	20	750 mg	Double-blind placebo controlled	12–48	Y	N	Y
De Maria *et al.*[184]	1996	59	600 mg	Double-blind placebo controlled	24	N	Not done	Not done
Lindor[185]	1997	105	13–15	Double-blind placebo controlled	34	Y	N	N
van Hoogstraten *et al.*[186]	1998	48	10	Double-blind	24	Y	N	Not done
Mitchell *et al.*[2]	2001	26	20–25	Double-blind placebo controlled	24	Y	N	Y
Harnois *et al.*[3]	2001	30	25–30	Open-label	12	Y	Not done	Not done
Okolicsanyi *et al.*[60]	2003	86	8–13	Double-blind placebo controlled		Y	Y	N
Olsson *et al.*[62]	2004	110	17–23	Double-blind placebo controlled	60	Y	N	Not done

Cullen S *APT* 2005

Immunosupression in PSC

- Steroids

  No significant effect

- Methotrexate

  3 small trials- no added effect over UDCA

- Azathioprine

  No published Trials

- Ciclosporin

  One RCT 2yrs 34pts- prevented histological progression but no improvement in LFT's

Immunosupression in PSC

- Tacrolimus

  One study of 10 pts, improved LFT's but progression not assessed

- Mycophenolate Mofetil

  One small trial –Mayo 30 pts 1 yr- no significant effect

- Metronidazole 6-800mg + UDCA 15mg/kg

  80 pts- MTZ sig improved ALP but no significant effect on progression

- Colchicine, Penicillamine, Etanercept, Nicotine

  No significant effects

Immunosupression in PSC

- Combination Rx
  - UDCA 500-750/d +
  - Prednisolone 1mg/kg/d +
  - Azathioprine 1-1.5 mg/kg/d

  - Median 41 mo
  - All had biochemical improvement
  - 6/10 had histological improvement
  - Only 1/10 had radiological deterioration

Schramm et al *Ann Int Med* 1999

Biliary Strictures and Cholangiocarcinoma

Dominant Strictures

- Extrahepatic ducts
- Prevalence 35-45%
- Stenting or dilatation?

  Increasing evidence that dilatation>stenting

  Peterson *Am J Gast* 2001,Stiehl *J Hepatol* 2002
- Antibiotic prophylaxis

Dominant Strictures

Stiehl et al *Eur J Gastro Hepatol* 2006

- 50 patients (103 ERCP's)
- At ERCP 37 had a dominant stricture
- Culture of bile revealed 15/37 (40%) of those with DS were infected with enteric bacteria
- The 13 controls without a DS had sterile culture
- Positive cultures were associated with a significant deterioration in bilirubin over the following 7mo (median)

Dominant Strictures

Bjornsson et al *Am J Gast* 2004

- Natural Hx study
- ERCP's form 125 pts with PSC
- 56 (45%) dominant strictures
- No significant difference in ALP between those with and without a DS
- The change in ALP/Bili when comparing pre ERCP values to 2-12 mo post ERCP was not significantly different in those with and without a DS

Cholangiocarcinoma

- Prevalence 6-20%
- Incidence 1-5% / year
- Prediction is extremely difficult
- Independent risk factors
  - Clincal suspicion……..Cullen *APT* 2005
  - Recent diagnosis
  - No previous UDCA
  - Previous Colon Ca
  - Variceal bleeding…….Burak et al *Am J Gast* 2004
  - Proctocolectomy
  - Lack of symptoms

Cholangiocarcinoma

Investigation

- Dilated intrahepatic ducts on USS/ tumour compression or thrombosis of PV
- Mass on X-sectional imaging
- ERCP
- Brush Cytology
- Needle Biopsy
- ?EUS and Intraductal ultrasonography
- ?PET
- Ca19.9
    - Level >100 U/ml…. Sensitivity 75%, specificity 80%

Cholangiocarcinoma

Cytology

- High specificity and PPV (92-100%)
- Low sensitivity (50%) and NPV

- May be improve in future by molecular methods
  - Inactivated tumour supressor genes
  - Dysregulation of apoptosis

Surgical Management Options

- Reconstructive Surgeries
- Orthotopic Liver Transplant
- Supportive Management

Thank You !