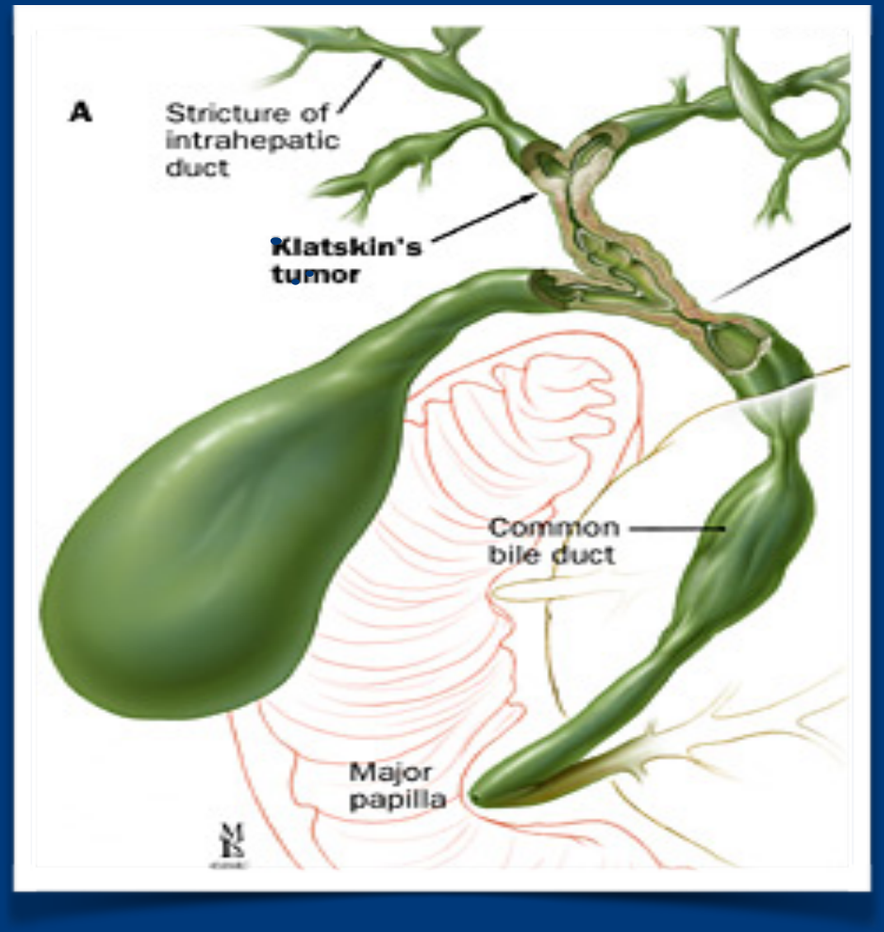
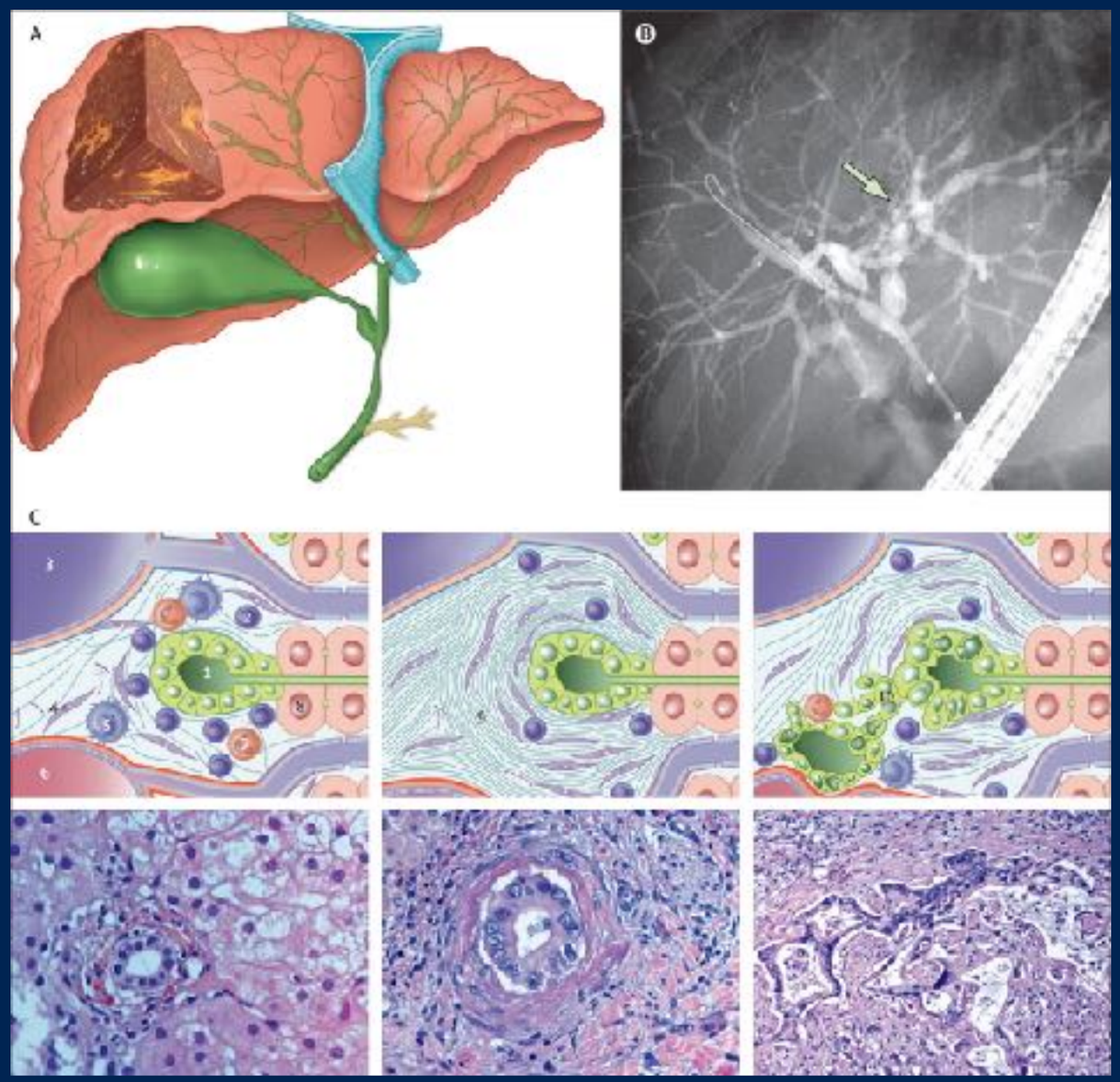
Colons, Cholangio's and Controversies



Bilal Bobat
Consultant Gastroenterologist
CMJAH and WDGMC

Overview

- Epidemiology
- Pathogenesis
- Natural History
- Diagnosis
- Treatment
- PSC and IBD

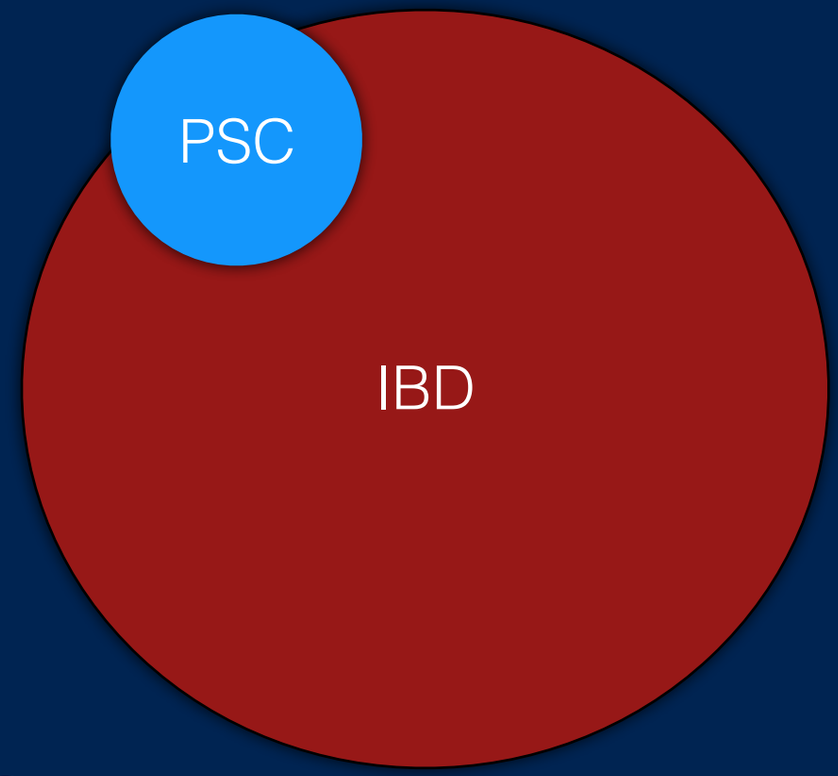


Primary Sclerosing Cholangitis

- Chronic Progressive Cholestatic Inflammatory
- Extra and Intra Hepatic Ducts
- Variable Rate of Progression
- Unclear Pathogenesis
- Poor Long term outcomes

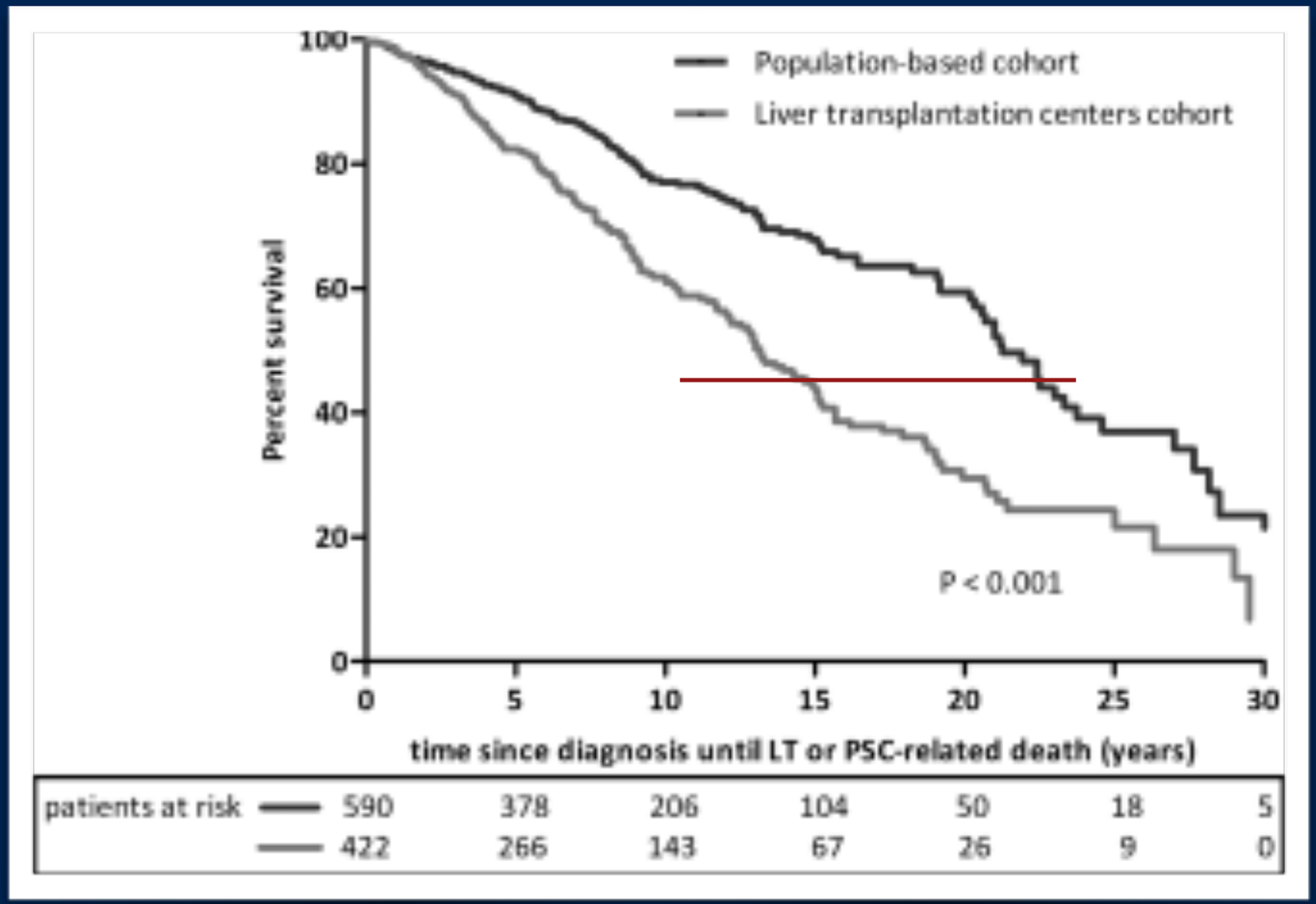
Epidemiology

- Incidence 1-3/100 000
- Prevalence of 16/100 000
- 60-70% Male
- Mean Age of Diagnosis 30-40 years
- Strongly associated with IBD
    - Conversely 4-5% of IBD associated with PSC



Natural History

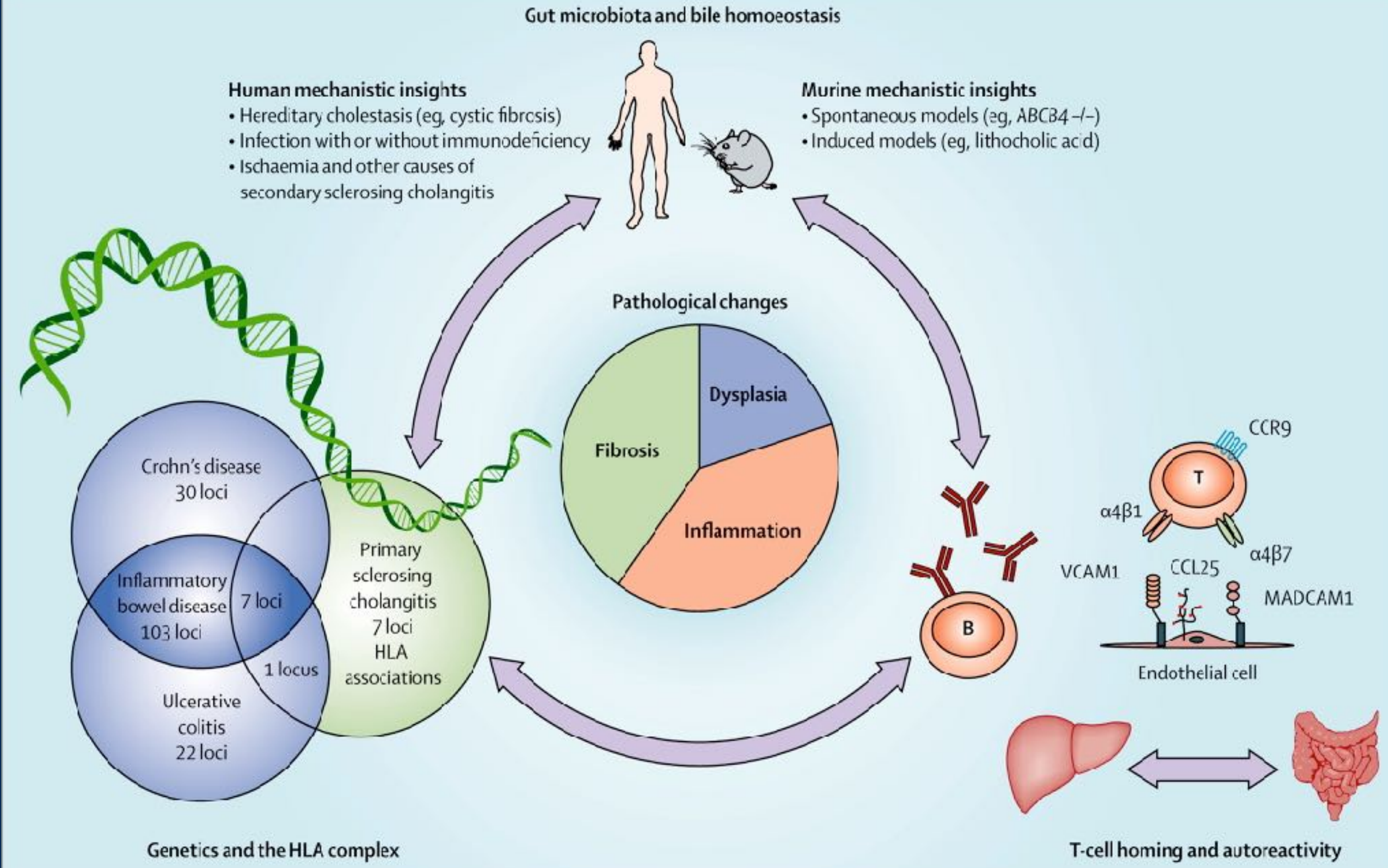
Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis



Hepatology
Volume 58, Issue 6, pages 2045-2055, 17 OCT 2013 DOI: 10.1002/hep.26565

Pathogenesis

- Genetics
- Microbiome
- Toxic Bile Theory
- Macrophage changes and Leucocyte Trafficking


Gut microbiota and bile homoeostasis
Human mechanistic insights
• Hereditary cholestasis (eg, cystic fibrosis)
• Infection with or without immunodeficiency
• Ischaemia and other causes of secondary sclerosing cholangitis
Murine mechanistic insights
• Spontaneous models (eg, ABCB4 –/–)
• Induced models (eg, lithocholic acid)
Pathological changes
Dysplasia
Fibrosis
Inflammation
Crohn's disease 30 loci
Inflammatory bowel disease 103 loci
7 loci
1 locus
Ulcerative colitis 22 loci
Primary sclerosing cholangitis 7 loci
HLA associations
B
CCR9
T
α4β1
α4β7
VCAM1
CCL25
MADCAM1
Endothelial cell
Genetics and the HLA complex
T-cell homing and autoreactivity

Diagnosis

Cholestasis → Cholangiogram → Liver Biopsy

- Elevated Alk Phos
- Auto Antibodies
- AMA
- IgG/IgM
- IgG_4

ERCP vs MRCP

- Beading and Stricturing

- Not Recommended
- Small Duct PSC
- Overlap Syndromes

Differential Diagnosis

Choledocholithiasis
Cholangiocarcinoma
HIV assoc. Cholangiopathy
IgG_4 Related Cholangitis
Portal Hypertensive Bilopathy
Diffuse Intrahepatic SOL
Surgical Biliary Trauma
Recurrent Pyogenic Cholangitis
Recurrent Pancreatitis
Sclerosing cholangitis in the critically ill
Intra-arterial chemotherapy

PSC vs IgG_4 Disease

	PSC	**IgG_4 Disease**
Male	65%	80%
Age	25-45yrs	65yrs
IBD	+	-
Jaundice	End Stage	Presenting Sympt 75%
Other Organs	-	+
IgG_4	9%	70%
Steroid	No Response	Dramatic Response
CCA	+	-

Medical Management

There is No Established

Medical Therapy!

Role of UDCA

Low Dose
13-15mg/kg/day

Improves Biochem
No Survival Benefit

Medium Dose
17-23mg/kg/day

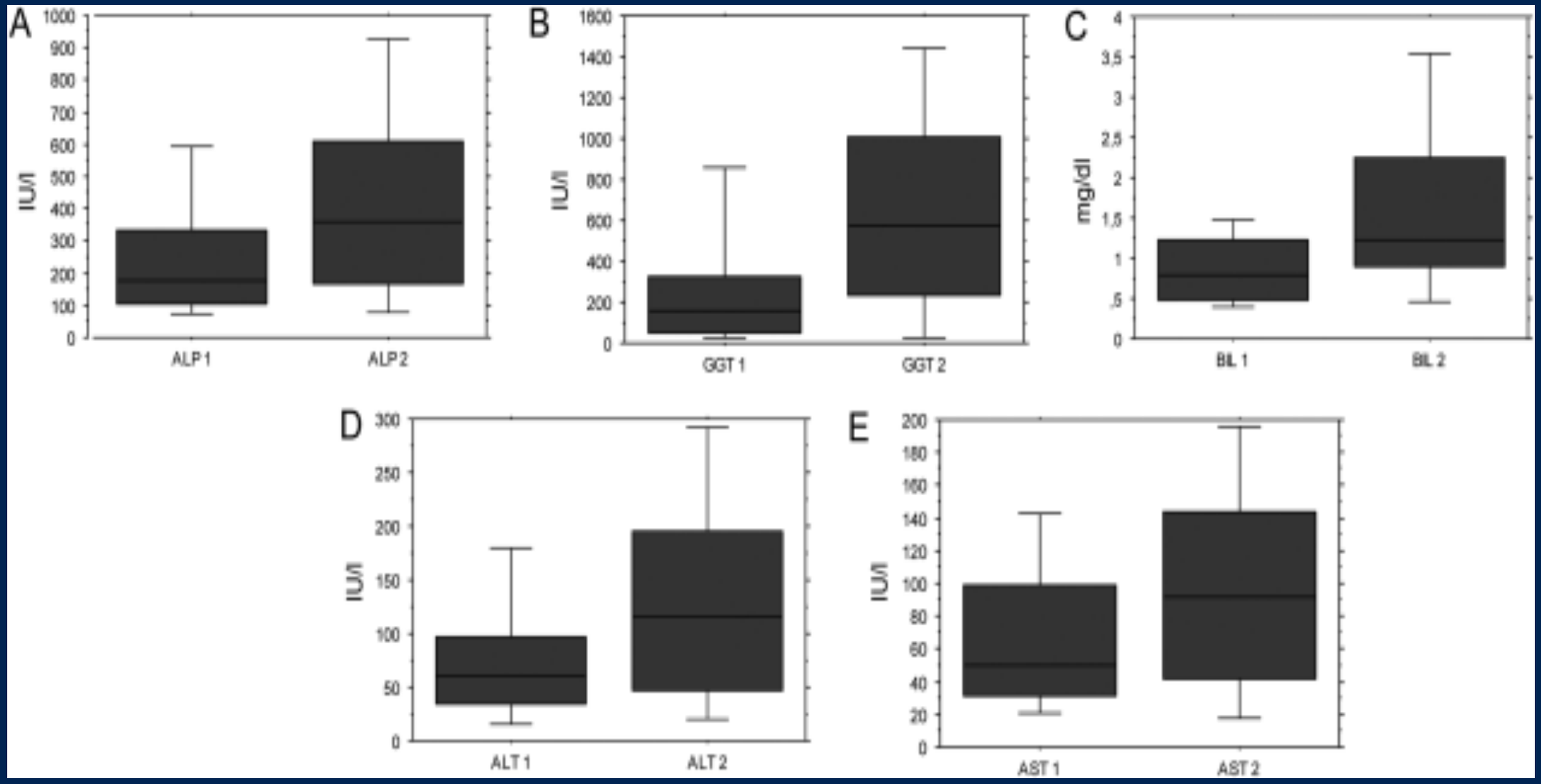
Improves Biochem
Trend towards
Survival Benefit
Study
underpowered

High Dose
25-30mg/kg/day

Increased rates
of Treatment
failure

Lindor K.D, NEJM 1997; Mitchell SA et al Gastro 200; Harnois et al Am J Gastroent 2001; Olsson R et al Gastro 2005; Lindor KD Hepatology 2009

Prospective evaluation of ursodeoxycholic acid withdrawal in patients with primary sclerosing cholangitis - Wunsch et al



Hepatology
Volume 60, Issue 3, pages 931-940, 30 JUL 2014

ACG 2015 Guideline

"More recently, several studies have shown that patients with PSC, who normalize liver biochemistries, whether this occurs spontaneously or more often with UDCA therapy, have a better prognosis. This has led some to revisit the issue of UCDA treatment for PSC; many practitioners are using a dose of ~20 mg/kg/ day, although data from well-controlled clinical trials are lacking (47–49)."

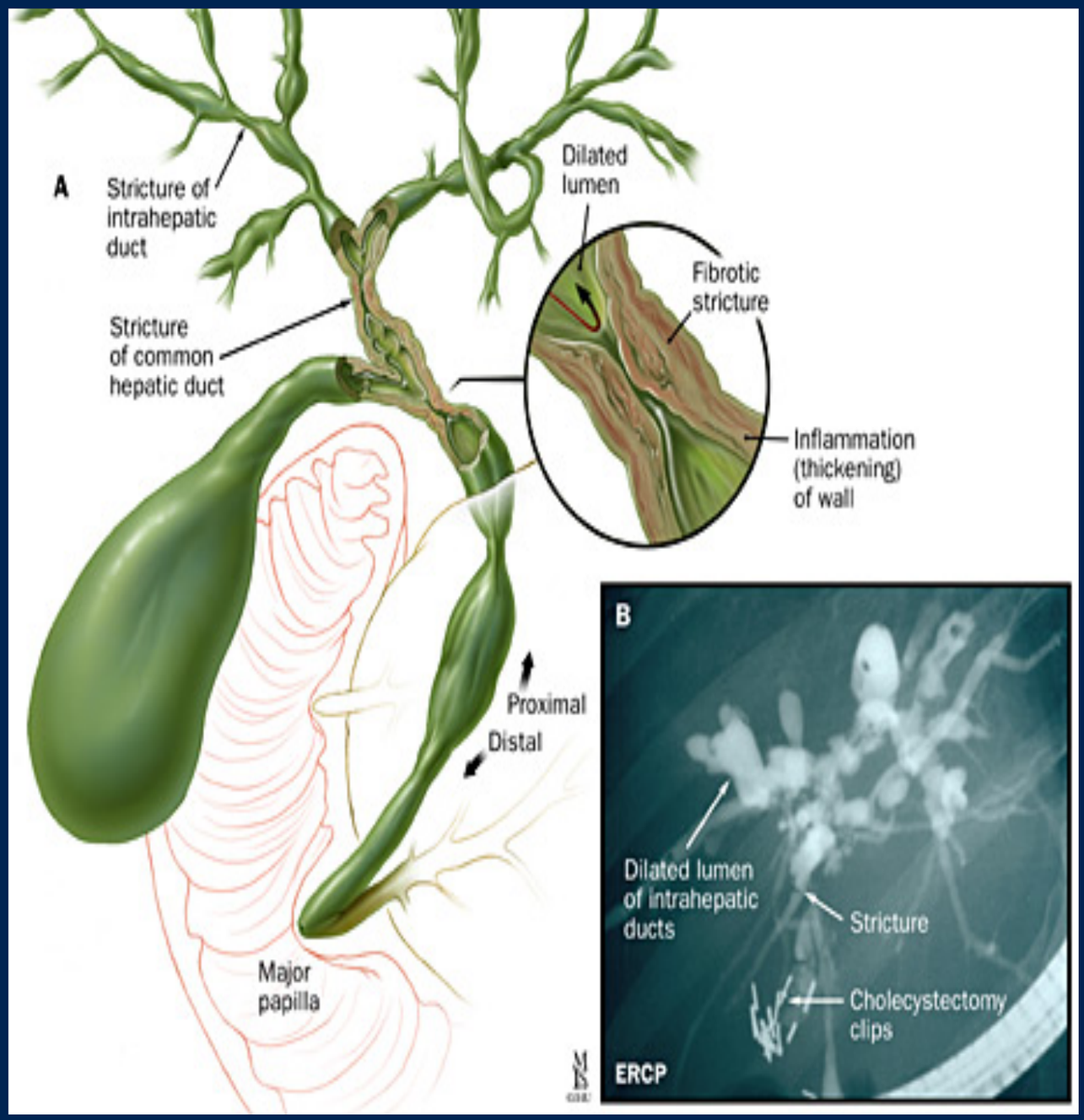
Lindor KD et al, AJG 2015

General Measures

- Pruritus: Step up approach
    - Bile Acid Resins/Rifampin/Naltrexone/Sertraline
- Monitor for Varices/Osteoporosis
- Fat Soluble Vitamin Deficiencies
- Refer for Liver Transplant
    - Decompensated Liver Disease
    - PSC Mayo Risk Score >2

Complications

- Dominant Strictures
- Cholangitis
- Malignancy



Screening
Cholangiocarcinoma

- Cross sectional Imaging every 6-12 months
  - US/CT/MRI
  - Ca 19-9
- MRI + Ca19-9 Sens 100% Spec 38%
- US + Ca 19-9 Sens 91% Spec 62%
- Cytology + FISH
- Cholangioscopy

Screening

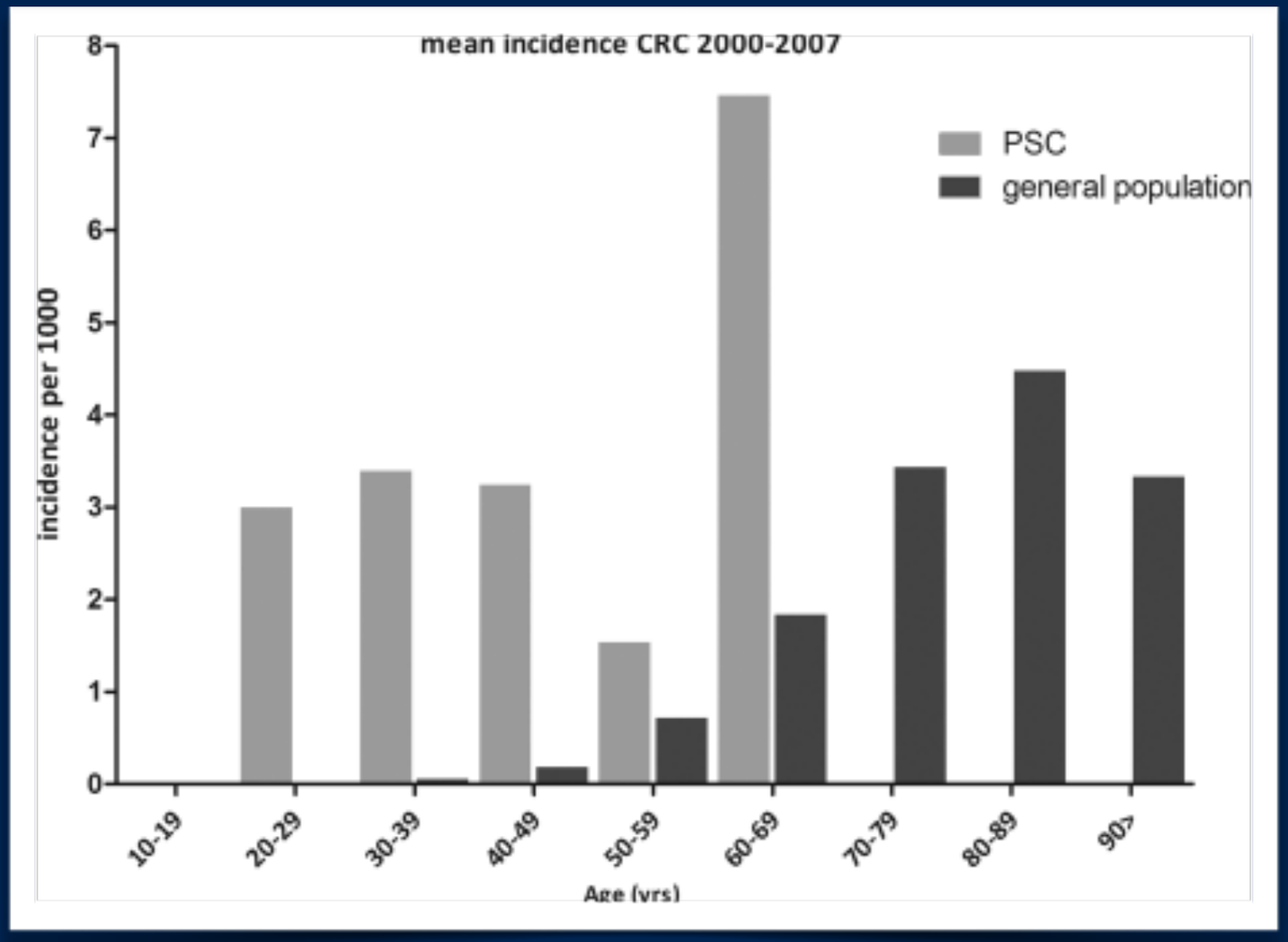
Gall bladder CA

- Polyps > 8mm in the gall bladder should result in Cholecystectomy

Lindor KD et al, AJG 2015

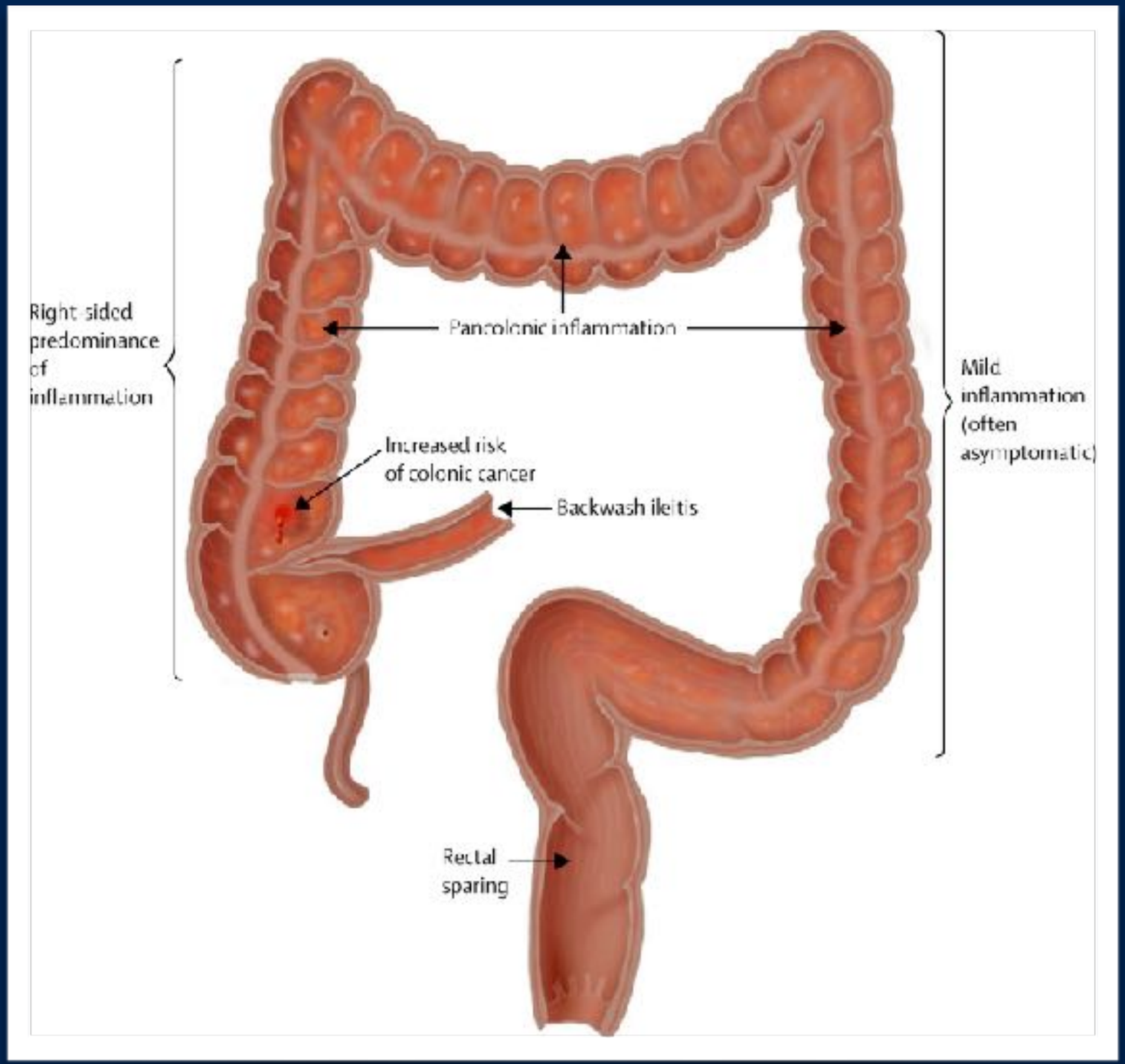
Screening
Colon

- Colonoscopy at Diagnosis
- Annual Colonoscopy if Concurrent IBD
- Every 3-5 years if no IBD
- Chromoendoscopy



Hepatology
Volume 58, Issue 6, pages 2045-2055, 17 OCT 2013 DOI: 10.1002/hep.26565
http://onlinelibrary.wiley.com/doi/10.1002/hep.26565/full#hep26565-fig-0005

PSC and IBD



The Lancet 2013 382, 1587-1599DOI: (10.1016/S0140-6736(13)60096-3)

Non PSC Liver Disease in IBD

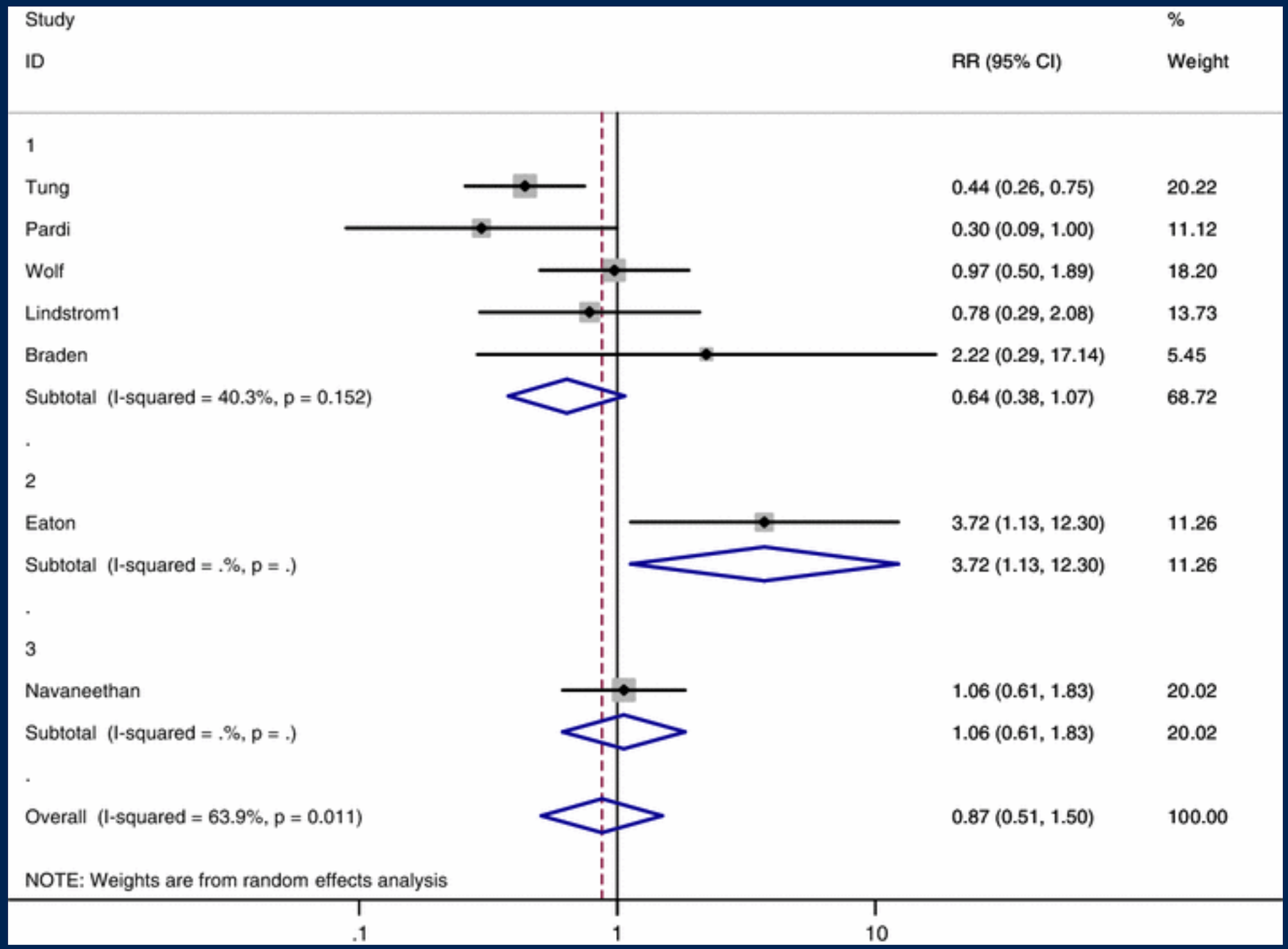
- NAFLD
- DILI
- Portal Vein Thrombosis
- Hepatic Amyloidosis
- Granulomatous Hepatitis
- Hepatic Abscess

PSC IBD and CRC

- 4-5 x Greater risk than IBD alone
- Carcinomas are Right Sided
- Low Dose UDCA has possible benefit

Digestive Diseases and Sciences
November 2013, Volume 58, Issue 11, pp 3079–3087

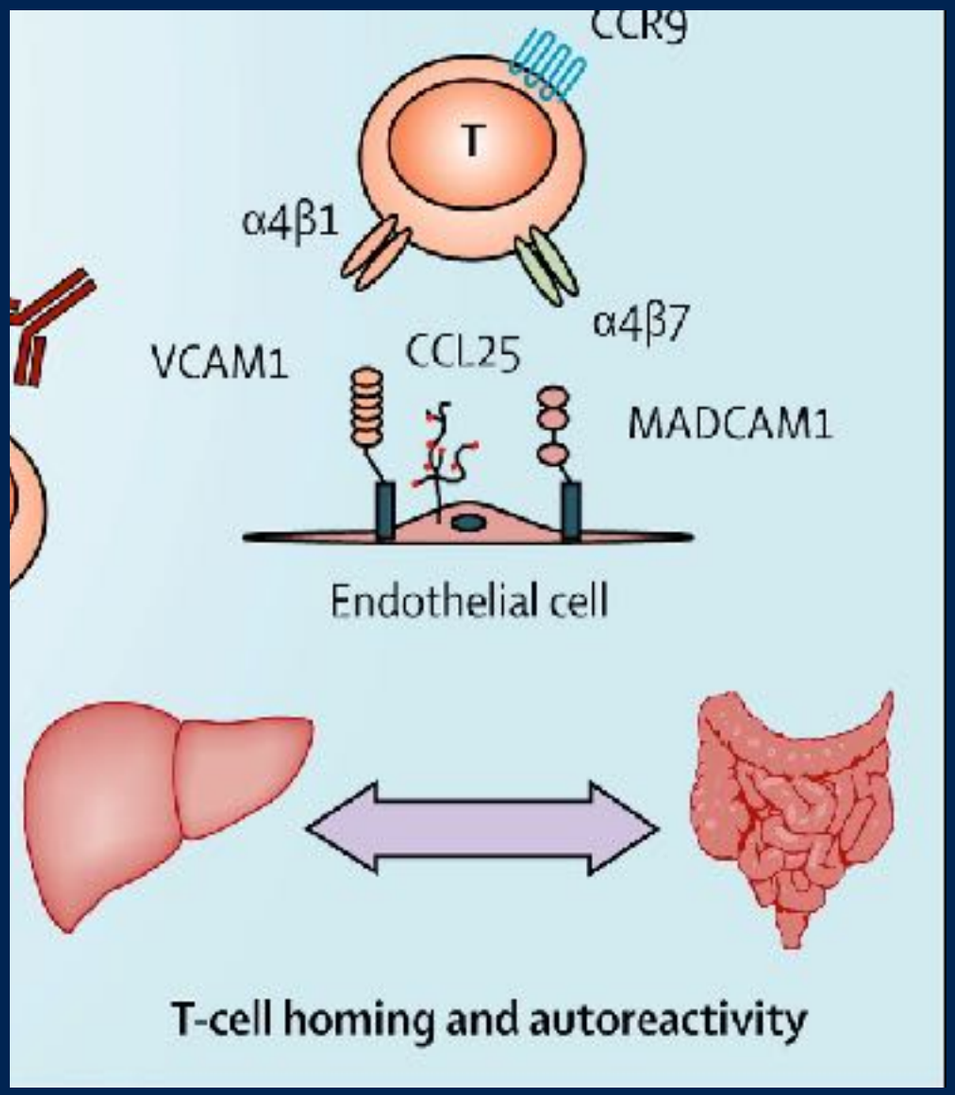
Ursodiol and Colorectal Cancer or Dysplasia Risk in Primary Sclerosing Cholangitis and Inflammatory Bowel Disease: A Meta-Analysis



Hansen, J.D., Kumar, S., Lo, WK. et al. Dig Dis Sci (2013) 58: 3079

Vedolizumab

- Monoclonal Antibody directed against $\alpha 4\beta 7$
- Decrease Leucocyte trafficking
- Other Novel Treatments include FXR agonists



The Lancet 2013 382, 1587-1599DOI: (10.1016/S0140-6736(13)60096-3)

In Conclusion

- At Diagnosis
  - Measure IgG4
  - Colonoscopy
  - Consider UDCA

- Follow up
  - Quarterly labs
  - 6-12 monthly Cross sectional imaging and Ca19-9

In Conclusion

- Dominant Strictures
  - ERCP with Brush Cytology and FISH
  - Dilatation

- Refer Liver Transplant
  - Clinical Decompensation
  - Suspicion of CCA

Roche

Slide ③

PSC - Chronic Progressive Cholestatic Inflammatory Dx
- Intra & Extra Hepatic Bile Ducts.
- Variable Rate of Progression
- Unclear Pathogenesis
- Poor Long Term Outcomes.

Slide ④⑤

Epidemiology
Incidence 1-3 / 100 000 / Prevalence 16 / 100 000
Male Prevalence 60-70%. Age 30-40 yrs.
Strongly Associated = IBD. - Predominantly UC but Also Crohn's
- Conversely 4-5% of IBD assoc c PSC.

Slide ⑤
Natural Hx :
Boonstra et al Published a large study from → 50% of Dutch Population.
Dutch PSC Database 44 Hospitals 3 Transplant Centres + Gen Pop Cohort.
Median Age Death or Tx 13 yrs Tx Centre.
Colon Malignancy. 22 yrs Gen Pop

Slide 6
Pathogenesis :
Not fully understood But Hereby using
Human Models = Cystic Fibrosis & Murine Models
have shed light

Slide 7
+ Genome Wide Association Studies have brought
16 Genes to our Attention. 7 - loci specifically
to PSC ; 8 loci assoc with IBD
HLA B8 DR3
× Toxic Bile Theory → Murine Models c Lithocolic Acid
× Abnormal Leucocyte Trafficking + Autoregulation in
the Bowel & Liver
× Microbiota

Slide (13) - 2013 Trial by Wungch et al set the
Cat amongst the Pigeons when they reviewed
Pts who had Discontinued UDCA Resulted in
Worsening of Enzymes and Symptoms.
ALP being used as Prognosticator - ↓/N ALP = better Outcomes.

Slide (14) - 2015 ACG Guideline led to this interesting Position
Statement

Slide (15) - General Measures
Bile Acid/Promethazine / Rifampicin 150-300mg. / SSRIs → Sertraline
Monitor - for Varices - Plt Count <150 000
- Adv Disease - Look for fat soluble Vitamins.
Refer for Liver Tx - Decompensated Dx / ? Earlier.
- PSC Mayo Score > 2. / MELD > 14.

Slide (16) Dominant Stricture : Stenosis <1.5mm in CBD or <1mm @ Hepatic
≈ 50% will have Dom Stricture @ Some Point.
22-26% Malignant
Poorer Survival excluding CCA ; ↑ ALP →
- Endoscopic Mx = Dilatation and Short Term Stenting
- Improved Mayo Risk Scores.

Cholangitis - Initial Presentation.
- R.F Dominant Strictures / Stones / Prior Endoscopic Inter
- Rx AB + Decompression.

Malignancy : 400 fold Greater Risk for CCA, vs Gen Pop.
50% Dx Early - 1st Year.
Cytology / +FISH ÷ Polysomy
Cholangioscopy ↑ available → Better Yields.

Slide (17)
Screening CCA : Cross Sectional HPB Imaging every 6-12 Months.
In Combination with Ca19-9

(18) Gall Bladder Ca : Polyps > 8mm -> Cholecystectomy
(19) Colon : Colonoscopy @ Dx then Annual if IBD or 3-5yrly
Hansen - Bornstein - Younger Dx CRC or low Dx.

Slide ~~(18)~~ (20) Thank you for indulging me.
- Yep I know its Not CT in December.
So lets talk a little about IBD.
PSC Phenotype : Mild Disease - often Quiescent. -> Broad Range of Assoc.
(R) Sided Dx ; Back wash ileitis and Rectal Sparing
But Bad Pouchitis following Ileal Pouch Anal Anastomosis.

Slide ~~(19)~~ (21)
Non PSC liver Dx

Slide (22) 4-5x Greater than IBD alone.
Ca RHS Low Dose UDCA Possible effect.

(23) Meta-analysis by Hansen : ≤ 25mg / ≥ 25mg
Low Dose Trend to Improvement
High Dose > 25mg/kg ? Harmful.

Slide (24) Vedolizumab - Monoclonal vs α4β7 - ↓ Leucocyte Trafficking Trafficking.
- Bernard Eksteen - Eg U.P Lead.
- Small study showed ? Dose -> ALP Improved.
- 20/4/17 - Study Withdrawn Clinical Clin Trials website.

FXR Agonists.
Cenicriviroc
Simtuzumab.
Norursodeoxycholic Acid
Altering Microbiome

Slide (8)
Diagnosis

Pruritis
1st Episode of Cholangitis.

- Cholestasis - ↑ALP . May be incidental ⇒ Insurance forms.
  - Additional tests : ANA Antismooth Muscle ANCA ⊕.
    - ANCA ⊕ - 97% confidence ⇒ PSC
    - Elevated Immunoglobulins IgG / IgM ⇒ ↑IgG4 - 10% Sufferers.

- Cholangiogram : Most Guidelines ⇒ MRCP ∴ - Similarly Accurate
  - Non Invasive
  - No Radiation.
  - ERCP - Better Sensitivity esp for small Peripheral Ducts.
    - Allows for Intervention.
  - Either way looking for Beading + Stricturing Appearance.

- Liver Biopsy - Not Recommended to make the Diagnosis.
  - Unless - ? Small Duct PSC / overlap Conditions.

Slide (9) PSC is still a Diagnosis of Exclusion and some of these Conditions should also be considered.

Slide (10) Differentiating Between PSC and IgG4 Disease is Important Because of the Dramatic Response Corticosteroid therapy either.
HISORT - Histology ; Imaging ; Serology ; Other Organs ; Response to Treatment

Slide (11) No official Medical Treatment.
- Especially since US trial using High Dose UDCA ⇒ Poorer outcomes
  Poorer outcomes included ↑ cancer ; Quicker Progression ⇒ Liver Tx / Decomp.
- Low Dose - Improves Biochem - No Survival Benefit.
- Med Dose : Scandinavian Group - Unable to Prove - Study 62% Enrollment achieved.
  But Increasing (?) is trend to Improved outcomes.