Updates in Autoimmune Hepatitis and PSC

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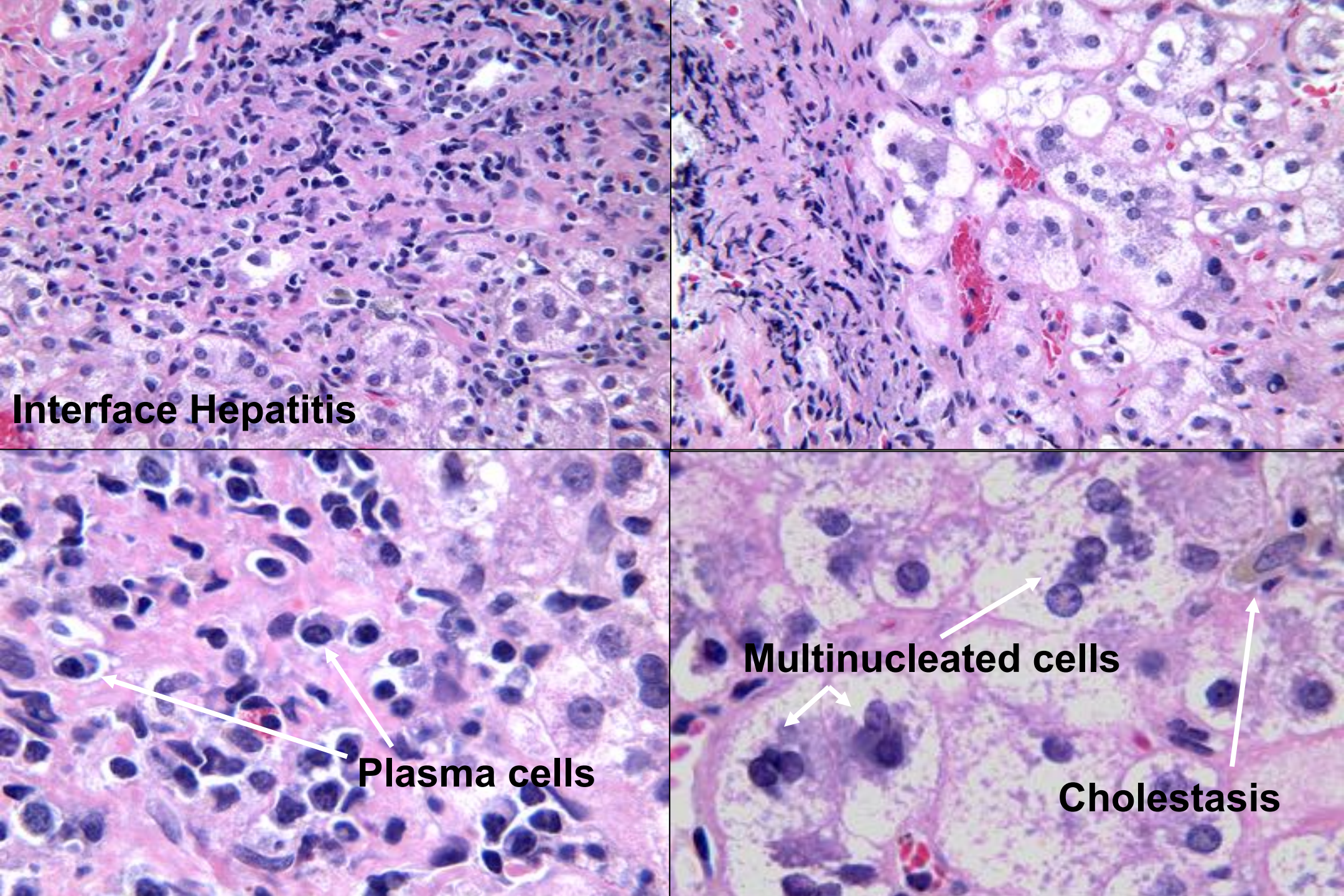
UCSF

6-3-17

Case

- Female Age 14
- Acute presentation of fatigue RUQ discomfort
- ALT 356; AST 307; Alkaline phosphatase 430; Bilirubin 0.6; INR 1.1; Albumin 3.7 Globulin 8.2
- Ceruloplasmin 29 IgG 2210 ANA 1:160, SMA 1:40
- Viral hepatitis A, B, C negative
- MRCP normal
- Liver biopsy plasma cells, piecemeal necrosis with some bile duct injury.


Interface Hepatitis
Plasma cells
Multinucleated cells
Cholestasis

Case: diagnosis

- Autoimmune Hepatitis:
  - Simplified score: IgG 2; AutoAb 2; no viral hep 2; biopsy 1 (consistent not diagnostic)
  - should not have abnormal bile ducts
- Autoimmune cholangiopathy
  - High IgG; Autoabs ANA pos; normal MRCP but pathology shows portal tract bile duct damage
- Treated with budesonide Cell cept normalized ALT.

Hennes 2008

Autoantibodies in AIH and Autoimmune cholangiopathy

	AIH	AIC
• ANA	95% (speckled)	~100% (diffuse)
• SMA	80%	50%
• Ig	IgG	IgG

- Liver biopsy- always ask about bile ducts
- Management - steroids mainstay
- - start with budesonide if not cirrhotic

Variable	Cut off	Points	Cut off	Points
ANA or SMA*	≥ 1:40	1	≥ 1:80	
LKM			≥ 1:40	2
SLA			positive	
IgG	>ULN	1	>1.1 x ULN	2
Histology	Compatible with AIH	1	Typical of AIH	2
Absence of viral hepatitis			yes	2
	Probable AIH*	6	**Definite AIH***	≥ 7

Hennes Hepatology 2008

AIH: Treatment

- Budesonide 3 mg tid- decrease to bid when ALT <ULN
- Prednisone 30-60 mg per day: 2mg/Kg/d
  - Monitor LFT's and IgG before every drop in prednisone
  - Decrease 10 mg per week till 30 mg
  - Decrease 5 mg/ 2-4 weeks
- √ TPMT if normal add Azathioprine 1-1.5 mg /kg /d
- Maintenance
  - Monitor LFTs, IgG and CBC 3 monthly
- Remission: clinical, biochemical, histological
  - 65% achieve remission by 18 mos, 80% by 2 y
- 50-86% relapse after withdrawal of Rx- common

AIH Relapse

Table 3. Patients' characteristics before treatment withdrawal.

Features	Relapse group, n = 13	Sustained remission group, n = 15
Median age at drug withdrawal, years (range)	41 (20-64)	39 (18-73)
Female, n	9 (69%)	11 (73%)
Concomitant autoimmune disease, n	3 (23%)	3 (20%)
Cirrhosis, n	2 (15%)	0
SMA, n	7 (54%)	10 (67%)
ANA, n	12 (92%)	12 (80%)
LKM, n	2 (15%)	0
SLA/LA, n	2 (15%)	0
Biopsy prior to withdrawal, n	5 (38%)	6 (40%)
Time to achieve initial remission, months (range)	5.3 (2-13)	2.7 (1-5)
Median ALT U/L (range)	20.1 (14-34)	14.7 (8-17)
Median IgG g/L (range)	12.7 (9.6-17)	10.3 (5.2-12)
γ-Globulin (range)	16.9% (14-20)	12.9% (7.8-18)

28 of 288 (10%) had treatment withdrawal

- All in remission at least 2 years on monotherapy
- No difference in labs at presentation

Hartl J Hep 2015

AIH: Who can stop Therapy?

- The minority of patients with AIH can sustain remission after treatment discontinuation (~ 5%)
- Classic AIH without overlap syndrome
- No cirrhosis
- Complete biochemical remission (normal ALT and IgG <1200 mg/dL) for at least 2 years on monotherapy
- All those in remission had ALT <0.5 ULN and IgG <1200 mg/dL

Pregnancy and AIH

- AIH is associated with adverse fetal outcomes
- Better maternal control improves fetal outcomes
  - Better AIH control with azathioprine or prednisone outweighs potential harmful effects of drugs on fetus
- Cirrhosis has increased fetal and maternal adverse effects
  - Should be managed by team of hepatologist/ endoscopist/obstetrician
- Close monitoring is required during pregnancy and post partum period for AIH flares which should be treated promptly

Impact of pregnancy on course of AIH

- De novo AIH in pregnancy reported, including fulminant presentation
- Flares during pregnancy occur in 7-21% pregnant women
  - Even in women who were in sustained remission
  - Flare are more likely to be associated with liver decompensation
- Flares post partum occur more frequently in 22-52%
- Higher Cesarean section rate in cirrhotic women
  - Often obstetrician choice with theoretically decreased risk of variceal bleeding but balance with higher risk of post operative decompensation

Heneghan 2001; Schramm 2006; Westbrook 2012; Steven 1979

Impact of Pregnancy on course of Cirrhotic AIH

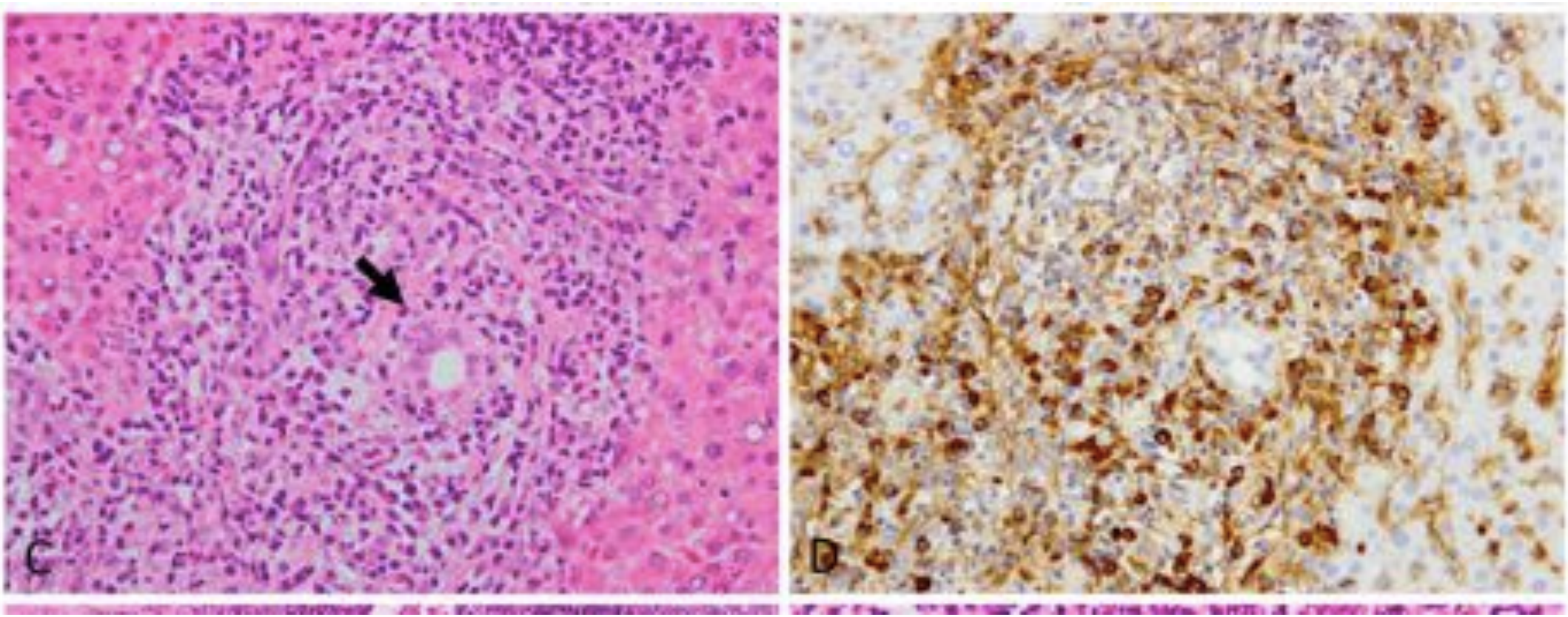
- Cirrhotic AIH patients have higher rate of liver decompensation
  - Worsening of portal hypertensive events
  - Propranolol not contraindicated
  - Higher serious maternal adverse event in cirrhotics (death or transplant in 9-11%)
  - In study of cirrhotic women, MELD>10 were more likely to have significant events: variceal bleeding, ascites and encephalopathy
  - Higher Cesarean section rate: not clear that this decreases risk of variceal bleeding

Westbrook 2010; Heneghan 2001; Schramm 2006; Westbrook 2012

Case age 19

- Increasing abdominal pain, epigastric
- Ultrasound sludge
- MRCP normal
- Cholecystectomy showed plasma cells
- IgG 4 169 (<86 mg%)
- IgG 2500 (<1600 mg%)
- Continued budesonide
- ALT 39; Alk Phos 138

IgG4 Autoimmune Biliary Injury



Case study

- Age 20 Loss of response to budesonide
- MRCP consistent with PSC
- Her MRCP age 22 showed classic PSC.
- Transition reported as young children mature

IgG4-**AIH vs PSC** Diagnosis

IgG4 Autoimmune Hepatitis

- Elevation of serum IgG4 concentration
- Coexistence of IgG4-related diseases except those of the biliary tract
- Characteristic liver biopsy
- Normal MRCP/ ERCP
- Effectiveness of steroid therapy

IgG4 Sclerosing Cholangitis

- Abnormal MRCP/ ERCP
- Elevation of serum IgG4 concentration
- Coexistence of IgG4-related diseases
- steroid therapy not often effective

Predictors of outcome in 7121 PSC patients

- 7121 patients in 37 centers in NA, Europe and Australia
  - 65.5% were men, 89.8% had classical or large-duct disease,
  - Small duct disease 3.4%; overlap PSC /AIH 6.6% (IgG4 excluded)
  - 70.0% developed IBD (56% UC, 11% CD)
  - Estimated survival overall 21 y
  - 2616 (37%) had LT or death (median time 14.5 years)
- 721 (10%)developed hepatopancreatobiliary malignancy (594 CCA). Incidence rate malignancy by age at diagnosis:
  - 1.2 per 100 py younger than 20 y; 6.0 per 100 py 21–30 y;
  - 9.0 per 100 py 31–40 y; 14.0 per 100 py 41– 50 y;
  - 15.2 per 100 py 51–60 y; 21.0 per 100 py > than 60 y.

Weismuller Gastro 2017

Predictors of outcome in 7121 PSC patients

Lower risk of LT and death and malignancy in

- Crohn's disease and no IBD (both vs ulcerative colitis)
- Small-duct PSC (P< .001) only 1/254 developed CCA
- Female sex P < .001, respectively).

Higher risk of LT and death and malignancy in ulcerative colitis compared with patients with

- Crohn's disease (HR, 1.56; P < .001)
- no IBD (HR, 1.15; P < .002)

Weismuller Gastro 2017

PSC and Cholangiocarcinoma (CCA)

- FISH on ERCP: polysomy >4 cells

102 patients without a mass lesion noted, an equivocal routine cytology, and 2 years of follow-up.

- 30 (29%) with an equivocal cytology result developed CCA within 2y
- CA 19-9 ≥ 129 U/mL (HR 3.19; P = .001); polysomy (HR 8.70; P < .001)
- Elevated CA 19-9 and polysomy were predictive of cancer (HR 10.92; P < .001) 10 patients.

- Patients without cytologic abnormalities were at minimal risk for the development of CCA.

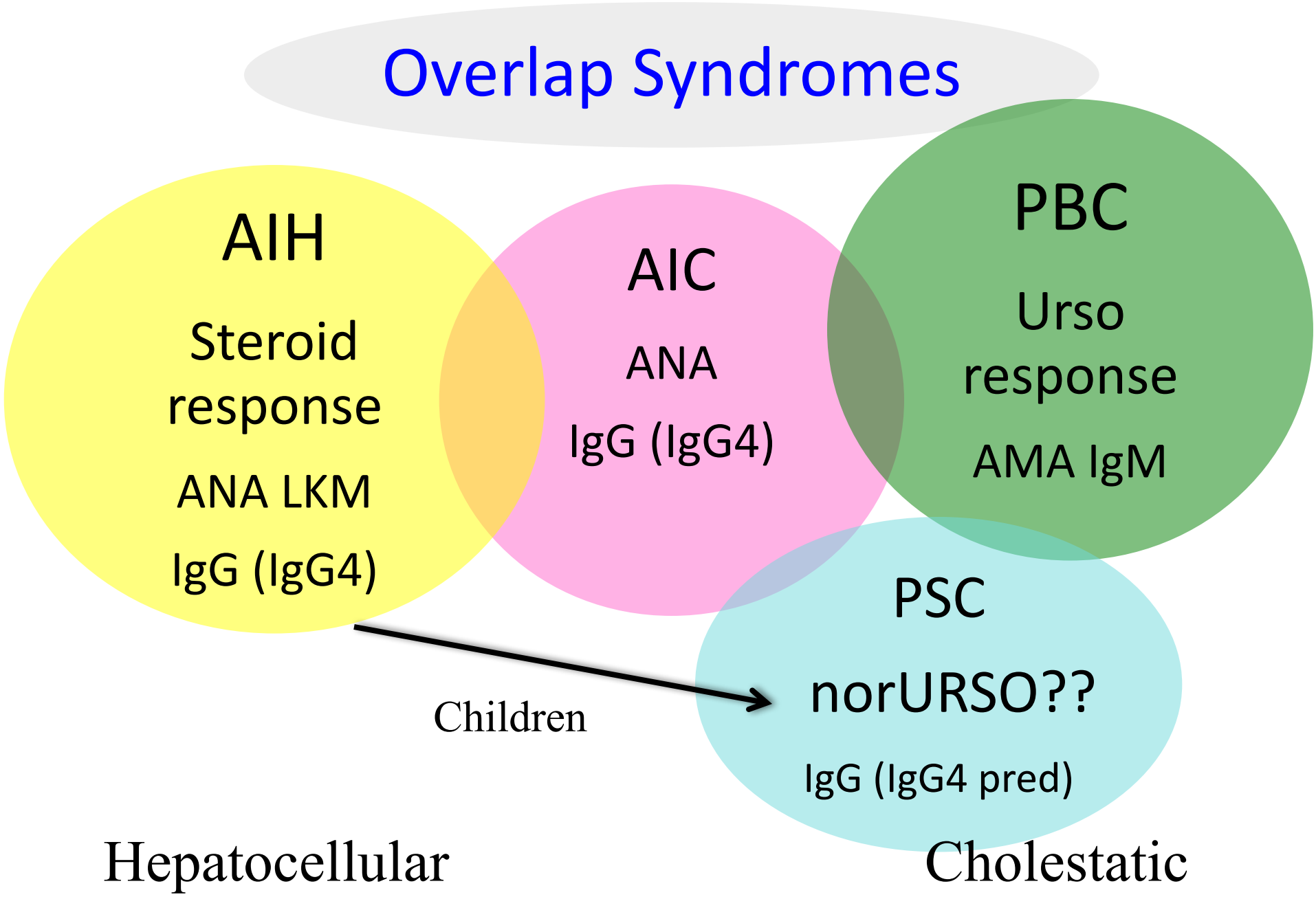
FISH polysomy meta-analysis 828 pts: sensitivity 68% specificity 70%*

Mayo 371 PSC pts with multifocal polysomy HR 82.42 for CCA

Fritcher cancer cytopath 2013;* meta analysis Navaneethan 2014; Eaton Am J Gastro 2015

Autoimmune Liver diseases

- Rule out viral hepatitis
- Screen ANA, SMA, IgG
  - Liver biopsy- AIH vs AIC
  - Test other Autoabs depending on age, labs
  - IgM if cholestatic
  - MRCP if cholestatic or young AIH
    - Follow alk phos and MRCP in young
  - IgG4
- Remember masses can be IgG4 not tumor of pancreas, bile ducts and liver


Overlap Syndromes
AIH
Steroid response
ANA LKM
IgG (IgG4)
AIC
ANA
IgG (IgG4)
PBC
Urso response
AMA IgM
PSC
norURSO??
IgG (IgG4 pred)
Children
Hepatocellular
Cholestatic