Autoimmune Hepatitis

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- **F/75**

- **P.I : 상기환자 황달로 타병원에서 본원으로 2018.6.25 방문하였고**
  Hx상 칡즙, 감기약 등 복용함.

- **CBC : 3,030>-11.9-<194K**
- **AST/ALT 450/144, ALP/R-GTP 122/123, TB/DB 16.3/9.0**

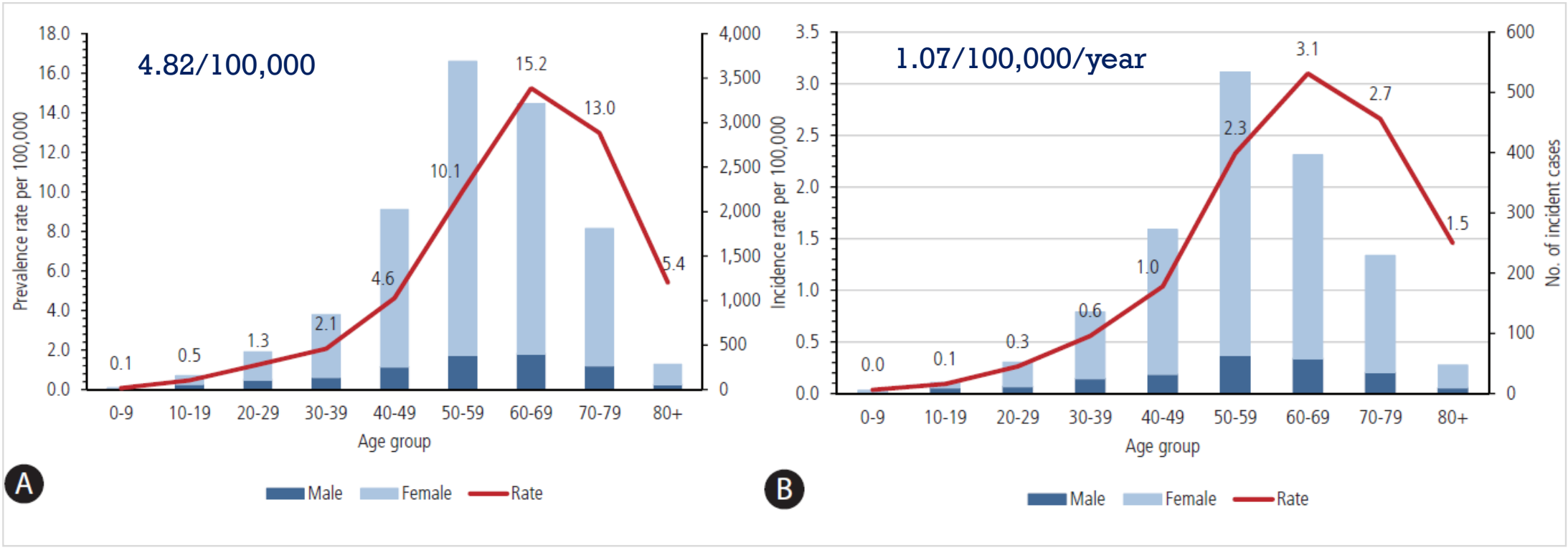
- **ABD U/S : Acute hepatopathy with mild splenomegaly. Cholangitis of liver.**

- **Viral marker) HBsAg/HBsAb/HCV-Ab(-/+/-) HCV-RNA : not detected**

Toxic hepatitis ?

Current epidemiology and clinical characteristics of autoimmune liver diseases in South Korea

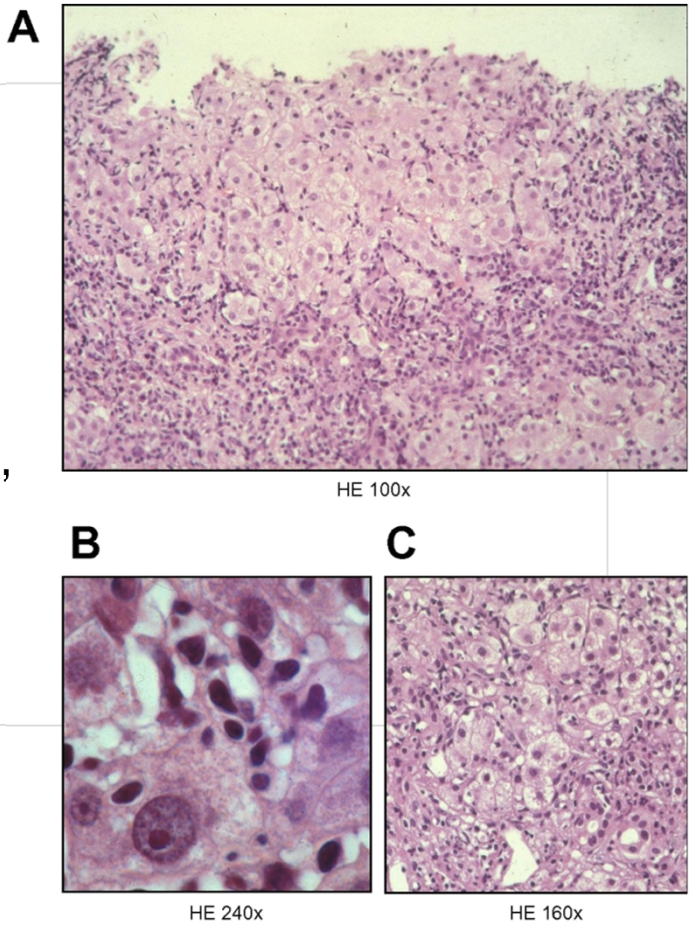
< The age-adjusted prevalence rate & incidence rate per 100,000 population (2009-2013) of AIH >



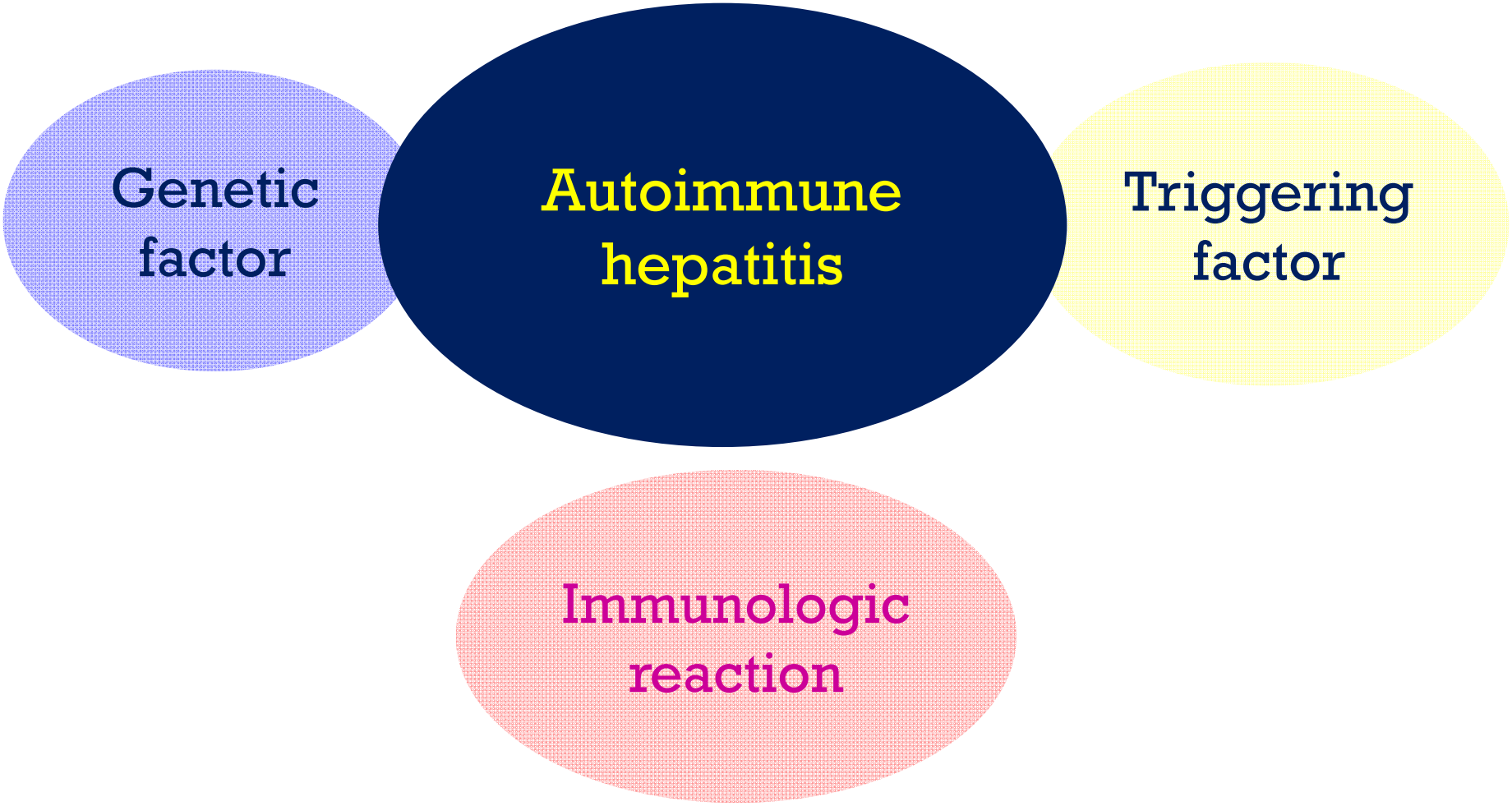
Clin Mol Hepatol 2018;24:10-19

Autoimmune Hepatitis

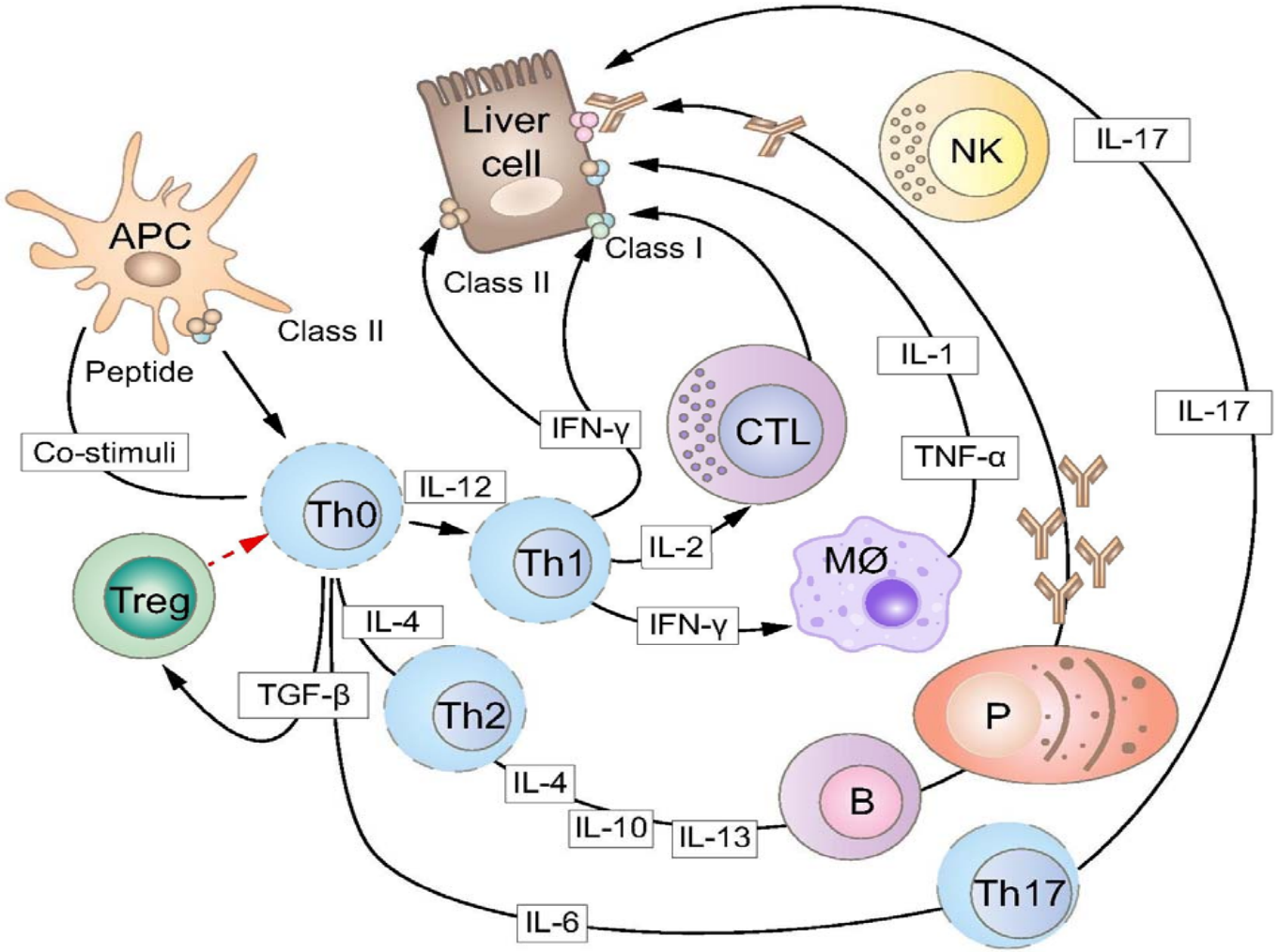
- Women
- Hypergammaglobulinemia
- Circulating autoantibodies
- Association with human leukocyte antigens (HLA) DR3 or DR4,
- Interface hepatitis on liver histology
- Favorable response to immunosuppression



Pathogenesis of AIH



Pathogenesis of AIH



J Hepatol 2015;63:971–1004

Content

- Clinical characteristics
- Diagnosis
- Treatment
  - Induction & Maintenance
  - Treatment in suboptimal response
  - Treatment in AIH combined with other liver disease

Clinical characteristics of AIH in South Korea

	KASL 1st Study	KASL 2nd Study	Single center study	RID analysis study
Stud				
Year				
Num				
Diag Defi				
Age				
Fem				
Cirrh Acut Asyr				
Hep				
Com	Hemolytic anemia, 1.2% Primary biliary cholangitis, 0.6%	Sjogren's syndrome, 8.0% Rheumatoid arthritis, 4.8% Raynaud's synd, 3.2% Systemic sclerosis, 2.4%	Rheumatoid arthritis, 0.3% Dyslipidemia 17.9% Primary biliary cholangitis, 7.4%	

- Any age & both sex were affected
- Broad range from asymptomatic to acute/severe or even fulminant
- insiduous onset (m/c)
- Acute onset (about 25%)
- Cirrhosis already present in 1/3 of patients at diagnosis
- AIH is associated with a broad variety of other autoimmune diseases

018;24:10-19

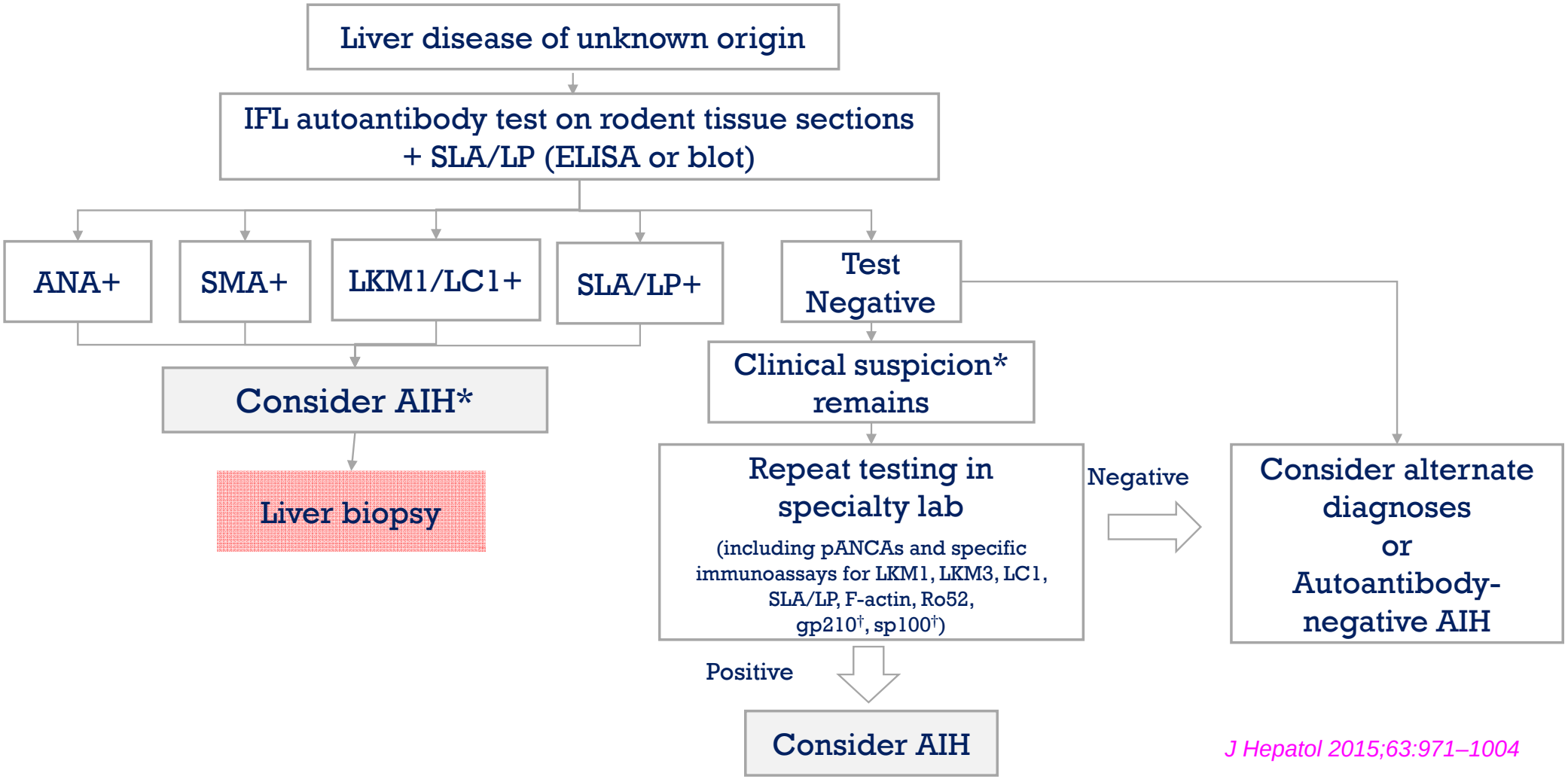
Clinical characteristics of AIH in South Korea

	KASL 1st Study Lee JH, et al.[6] (2004)	KASL 2nd Study Kim BH, et al.[7] (2013)	Single center study Kil JS, et al.[8] (2010)	RID analysis study Kim BH, et al.[2] (2017)
Autoantibody positive rate				Autoantibody testing rate
ANA	92%	94%	81.4%	93.9%
SMA	31%	23%	44.2%	81.7%
Anti-LKM1	1%	3%		88.4%
AMA	7%	11%	3.4%	67.5%
ALT (U/L), mean/median		284	/182 (31-1,251)	
Total bilirubin (mg/dL), mean/median		4.5	/2.3 (0.3-39)	
Immunoglobulin G (g/dL), mean/median	1.72 UNL	2,356 (1.4 UNL)	/2380 (1,330-4,640)	
Liver biopsy performed	74%	75.2% Interface hepatitis (86%) Plasma cell (58%) Rosette (15%) Septal fibrosis/cirrhosis (20%/5%)	70.9%	54.2%

Subclassfication of AIH based on autoantibody pattern

Sub-type	Features	
• AIH-1	• Almost 90% of AIH cases • Detection of ANAs, SMAs or anti-SLA/LP • Association with HLA DR3, DR4 and DR13 • Any age at onset • Variable clinical and histopathological severity	• Usually excellent treatment response, but variable relapse rates after drug withdrawal and need for long-term maintenance therapy
• AIH-2	• Up to 10% of AIH cases • Anti-LKM1, anti-LC1 and rarely anti-LKM3 • Association with HLA DR3 and DR7 • Onset usually in childhood/young adulthood • Clinical and histopathological severity commonly acute and advanced	• Sometimes failure of treatment and frequent relapse rates after drug withdrawal; need for long-term maintenance therapy very common
• AIH-3	• Up to 10% of cases • Only SLA/LP positive • Otherwise very similar to AIH-1* • Often Ro52-antibody positive	• Lifelong immuno-suppression in most, if not all patients

Suggested diagnostic algorithm for AIH



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IAIHG criteria for diagnosis (1999)

	Factor	Score
Gender	Female	+2
ALP:AST(or ALT) ratio	>3 1.5-3.0 <1.5	-2 0 +2
r-globulin or IgG (time above upper limit of nl)	>2 1.5-2.0 1.0-1.5 <1.0	+3 +2 +1
ANA, SMA, anti-LKM titer	>1:80 1:80 1:40 <1:40	+3 +2 +1
AMA	(+)	-4
Viral marker	(+) / (-)	-3 / +3
Hepatotoxic drug	Yes / No	-4 / +1
Alcohol	<25g/d / >60g/d	+2 / -2
Concurrent immune ds	Any nonhepatic ds of immune nature	+2
Other autoAb	Anti-SLA/LP, actin, LC1, pANCA	+2
Histologic feature	Interface hepatitis Plasma cells Rosettes None of above Biliary changes Atypical featues	+3 +1 +1 -5 -3 -3
HLA	DR3 or DR4	+1
Tx response	Remission alone Remission with relpase	+2 +3

❖ **Pretreatment score**

- **Define diagnosis > 15**
- **Probable diagnosis 10-15**

❖ **Posttreatment score**

- **Definite diagnosis > 17**
- **Probable diagnosis 12-17**

AIAHG report. J Hepatol 1999

IAIHG simplified scoring system (2008)

Feature/parameter	Discriminator	Score
Antibodies (max 2 points)		(0–2 points total)
ANA or SMA+	≥1:40	+1
ANA or SMA+	≥1:80	+2
or LKM+	≥1:40	+2
or SLA/LP+	Any titre	+2
IgG or γ-globulins level	>ULN	+1
	>1.1x ULN	+2
Liver histology (evidence of hepatitis is required)	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of viral hepatitis	No	0
	Yes	+2

Score ≥7 = Definite AIH

Score ≥6 = Probable AIH

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- **Viral marker) HBsAg/HBsAb/HCV-Ab(-/+/-) HCV-RNA : not detected**

AutoAb) IgG: 2783.4 mg/dL
ANA : 1: 320 dilution - homogenous + cytoplasm (mitochondria pattern)
MA (1: 100 dilution) : positive without M2 specificity

Liver, needle biopsy:

- Interface hepatitis, moderate to marked
- Frequent ballooning degeneration of hepatocytes and marked lobular inflammation with mild cholestasis
- Presence of bile duct damage with bile ductular proliferation and granulomatoid features
- Plasma cell infiltration in porto-periportal and lobular inflammatory cell infiltration

, R/O autoimmune liver disease

Category	Factor	Score
Gender	Female	☑ +2
Alk phos : AST[or ALT] ratio	>3	☐ -2
	<1.5	☑ +2
r-Globulin or IgG [times above upper limit of normal]	>2.0	☐ +3
	1.5-2.0	☑ +2
	1.0-1.5	☐ +1
	<1.0	☐ 0
ANA, SMA, or anti-LKM1 titers	>1:80	☑ +3
	1:80	☐ +2
	1:40	☐ +1
	<1:40	☐ 0
AMA	Positive	☑ -4
Viral makers of active infection	Positive	☐ -3
	Negative	☑ +3
Hepatotoxic drugs	Yes	☑ -4
	No	☐ +1
Alcohol	<25 g/d	☑ +2
	>60 g/d	☐ -2
Concurrent immune disease	Any nonhepatic disease of an immune nature	☐ +2
Other autoantibodies	Anti-SLA/LP, actin, LC1, pANCA	☐ +2
Histologic features	Interface hepatitis	☑ +3
	Plasma cells	☑ +1
	Rosettes	☐ +1
	None of above	☐ -5
	Biliary change	☑ -3
	Atypical features	☐ -3
HLA	DR3 or DR4	☐ +1
Treatment response	Remission alone	☐ +2
	Remission with relapse	☐ +3
Total		7

▪**score : 7**

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH
		≥7: definite AIH

▪**score : 6**

	2018/6/26	2018/06/29	2018/07/06	2018/07/20	2018/09/27
AST/ALT	450/144	376/91	89/37	47/24	34/11
TB/DB	16.3/9.0	15.7/9.1	9.2/4.9	5.3/2.3	1.6/0.5
ALP/GGT	122/123	108/86	59/64	64/54	49/15

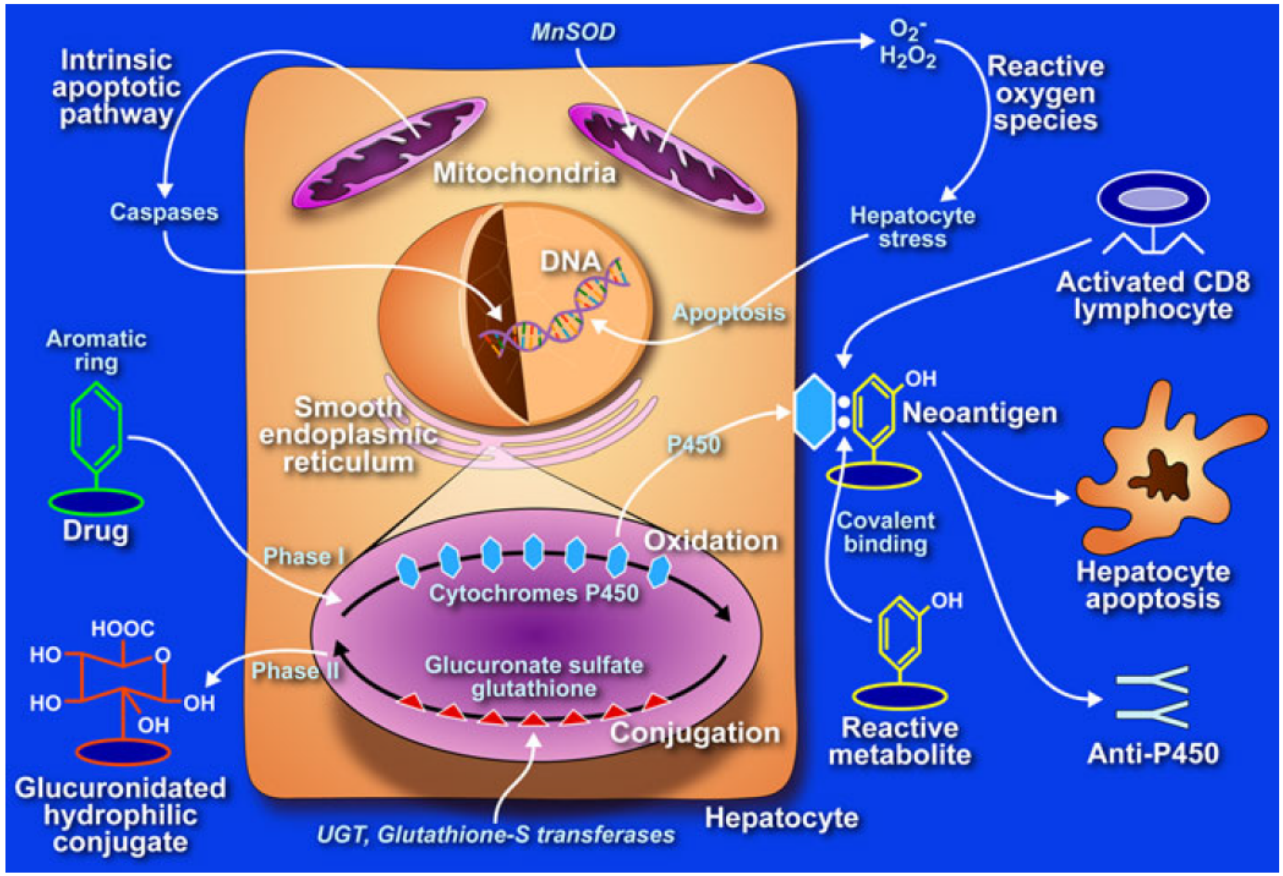
PRS 30mg/AZP 50mg start

Difficult to diagnose

- AutoAntibody negative AIH
- Acute/acute severe AIH
- DILI and AIH
- AIH with cholestatic feature

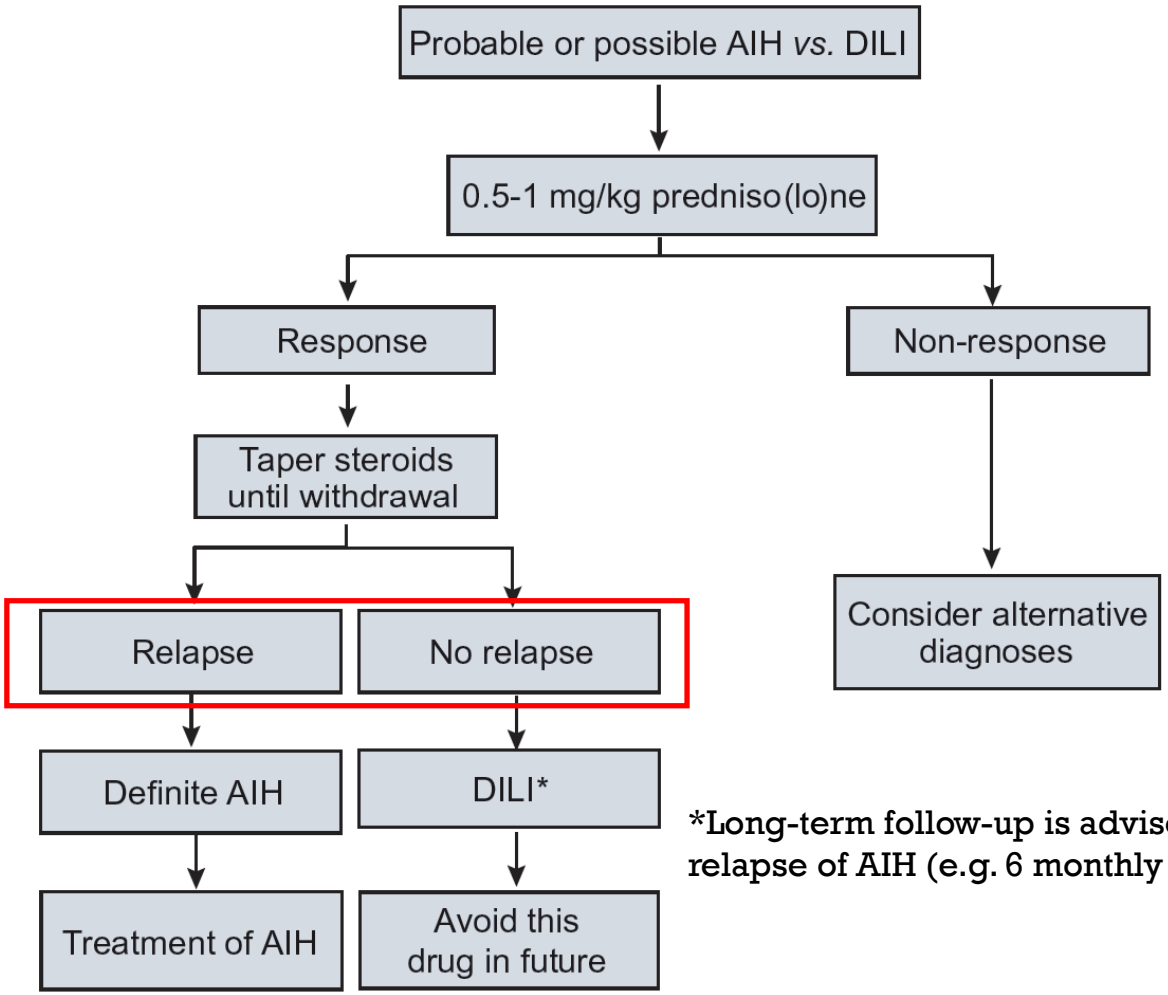
❖DILI & AIH

Putative pathogenic pathways of drug-induced immune-mediated liver injury



Dig Dis Sci (2011) 56:958–976

Management algorithm for drug-induced autoimmune like hepatitis



*Long-term follow-up is advised in order not to miss a late relapse of AIH (e.g. 6 monthly for 3 years)

J Hepatol 2015;63:971–1004

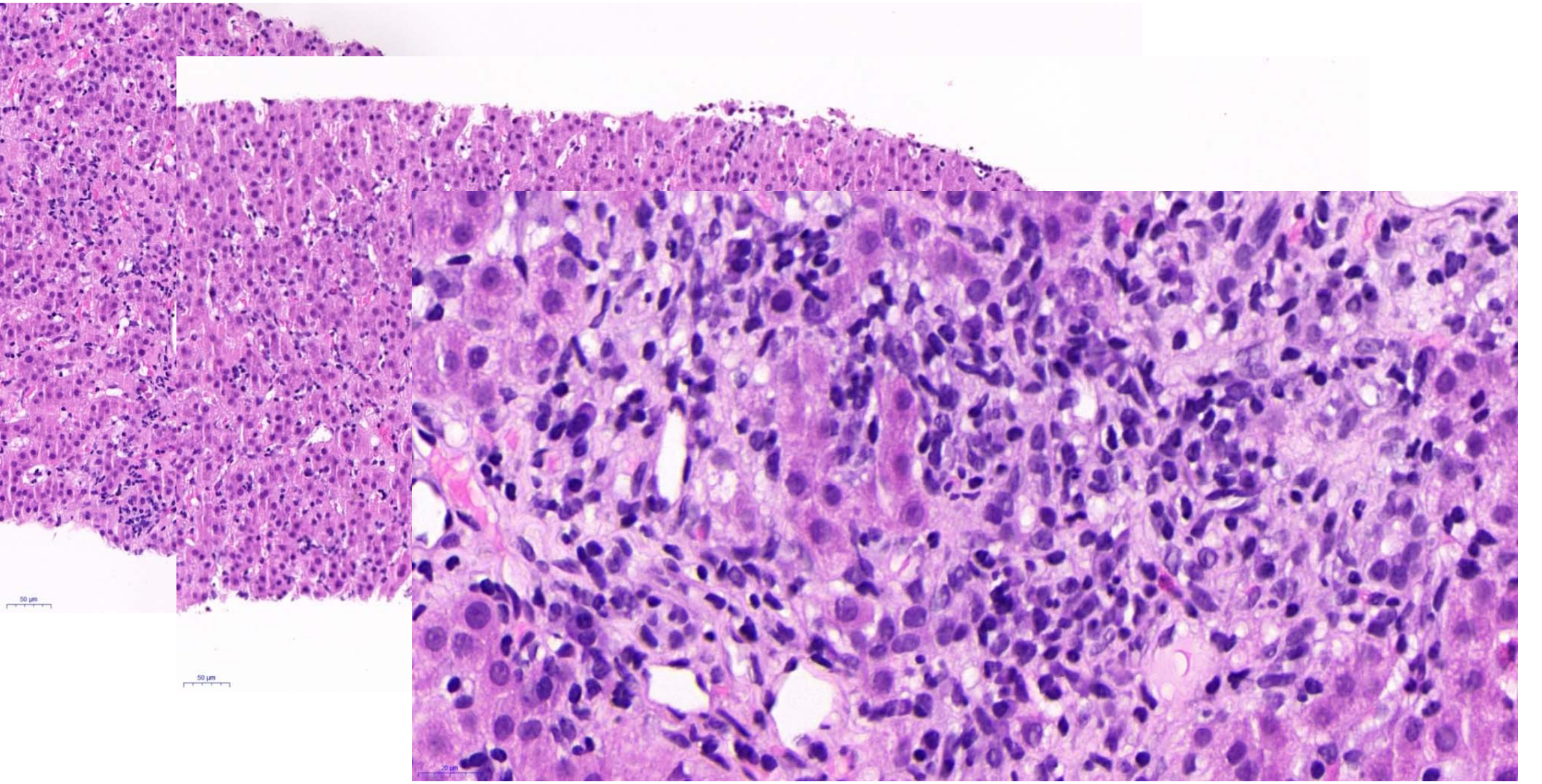
- **M/16**

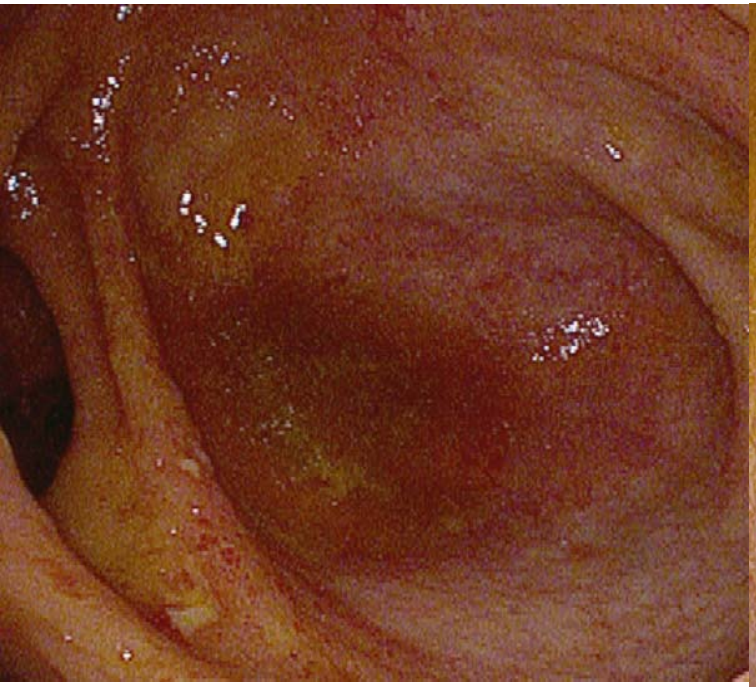
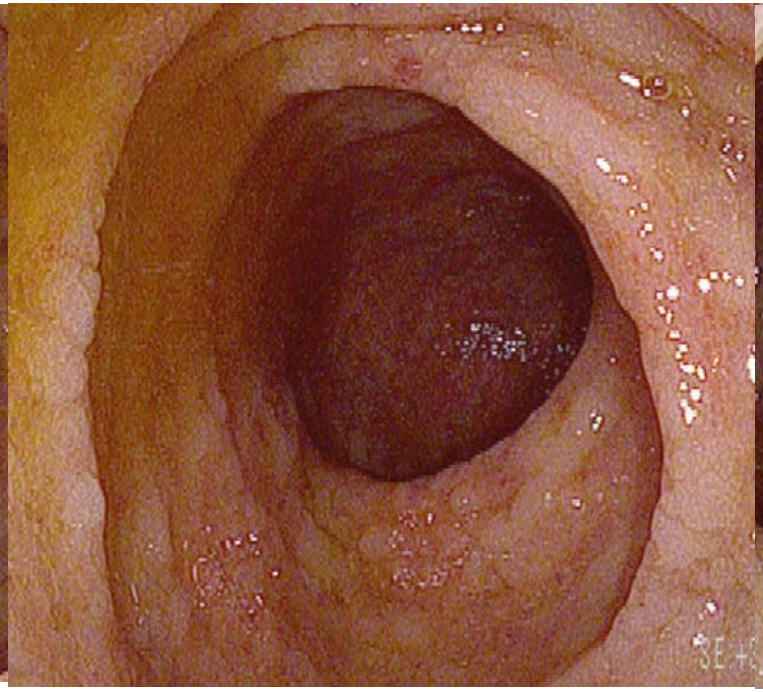
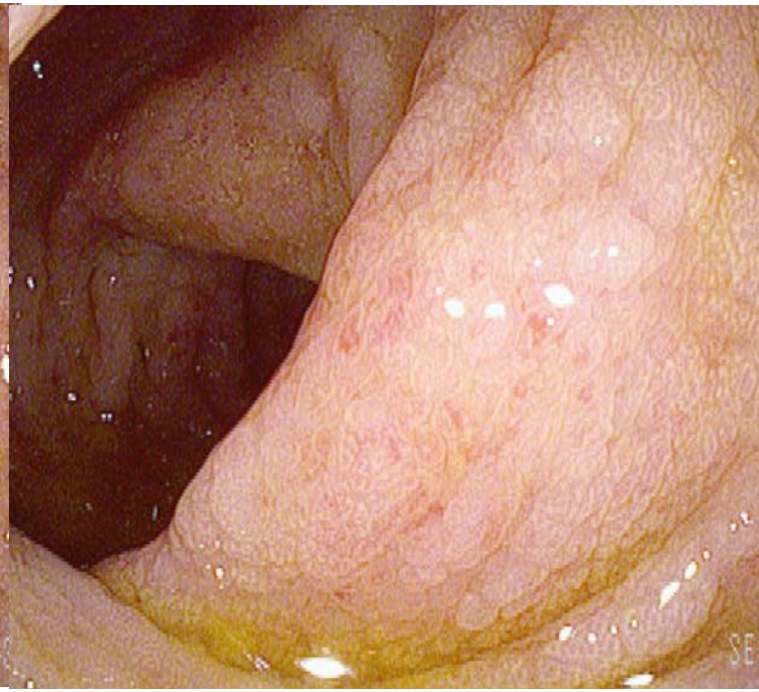
- **P.I : 상기환자 2013.5월 cellulitis로 타병원에서 치료 중 LFT상승으로 방문**

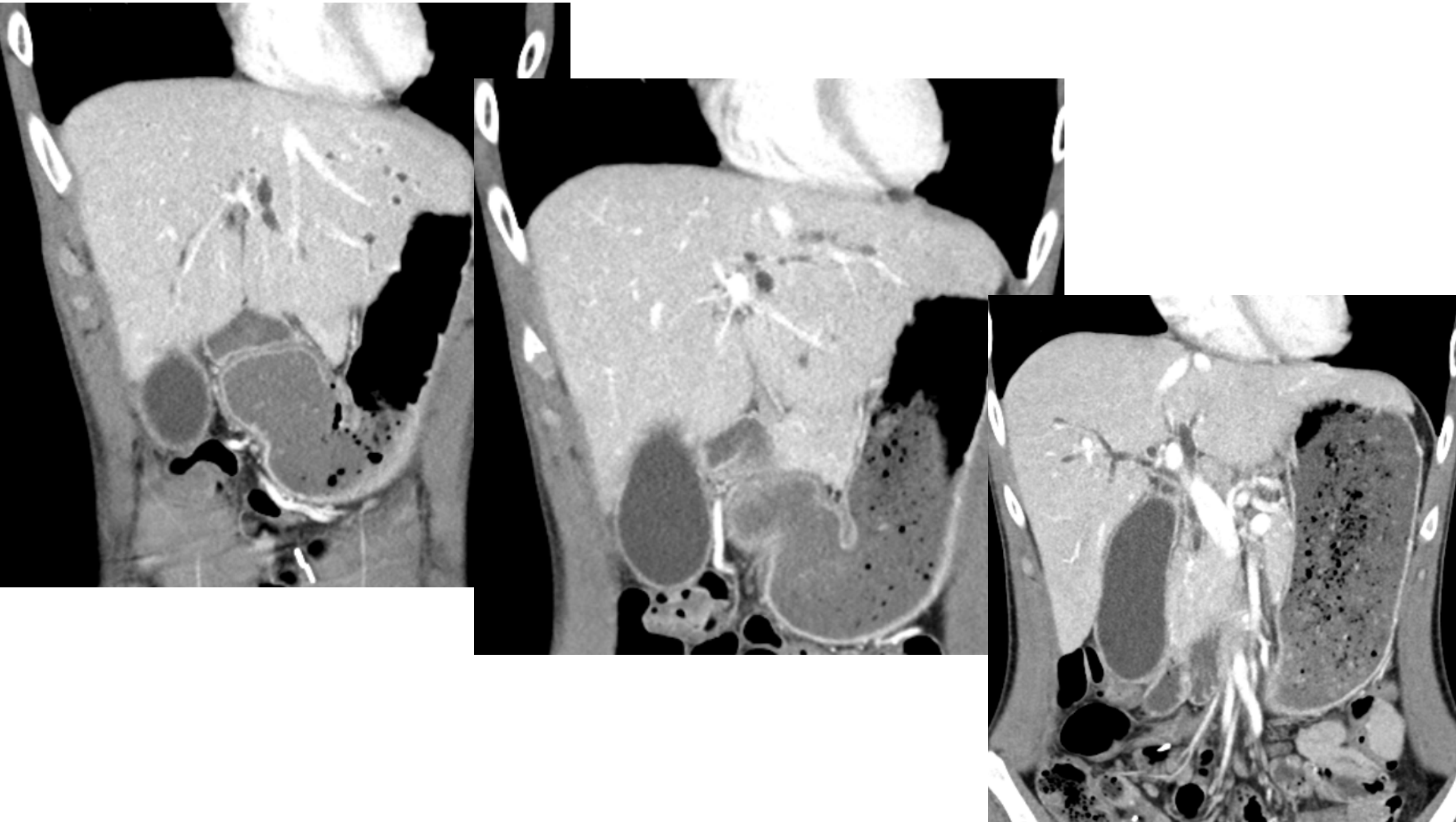
- **History taking : 한약 (+) 녹용 (+) : 3-4월까지, 항생제 (+)**
- **AST/ALT (13.4.28) 123/232 -> 13.5.12) 101/151, ALP/GGT 778/488**
- **Viral marker : N-S**

2달 뒤 지속되는 피로감, diarrhea
f/u AST/ALT 146/240, TB/DB 1.3/0.6, ALP/GGT 867/326

ANA 1:80 dilution - cytoplasm + nucleoplasm
AMA (1:100) positive without M2 specificity
SMA (1:100) positive
Anti-ds DNA 153.0 WHO unit/mL (moderate positive)


50 µm
50 µm
20 µm

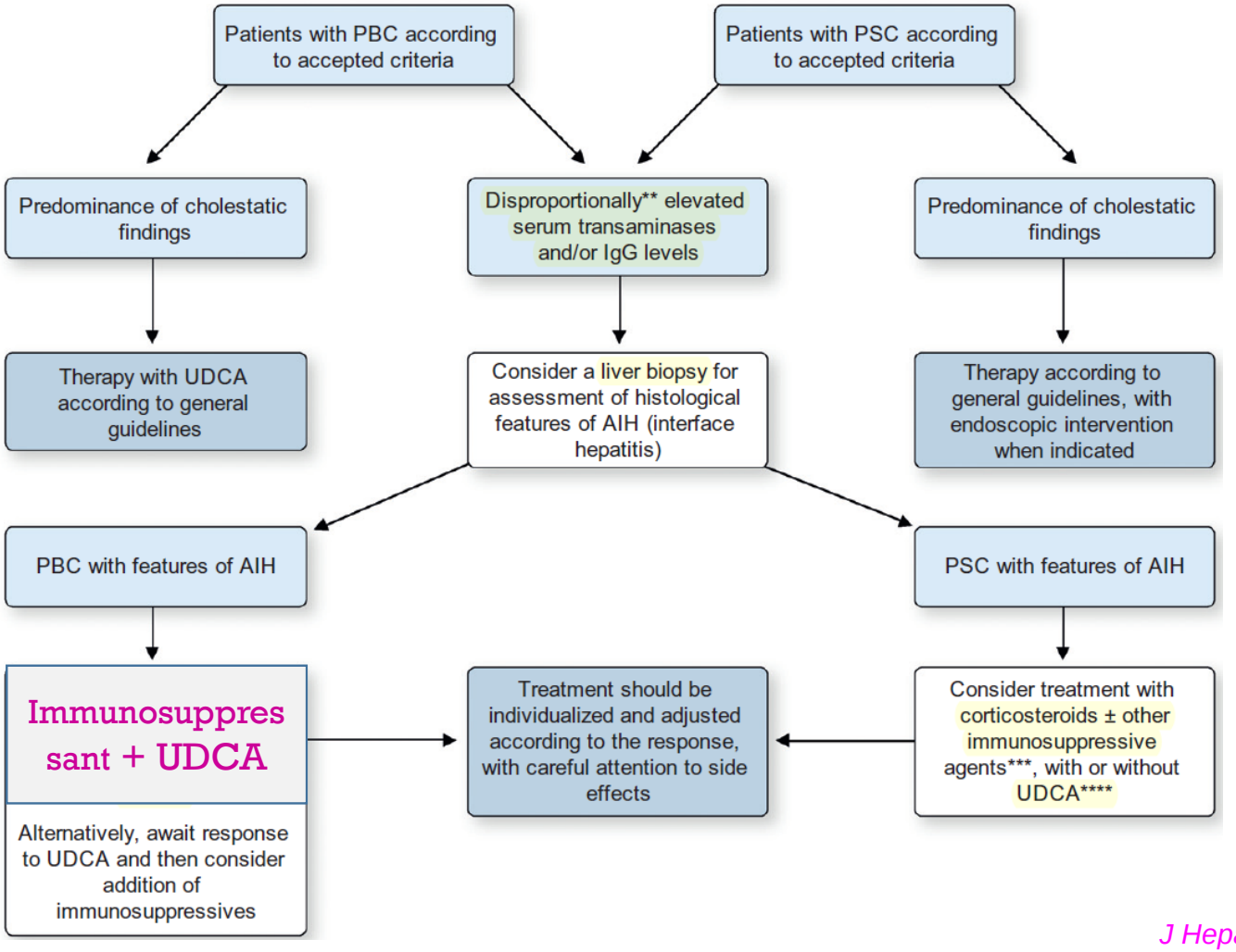






PSC with AIH feature UC

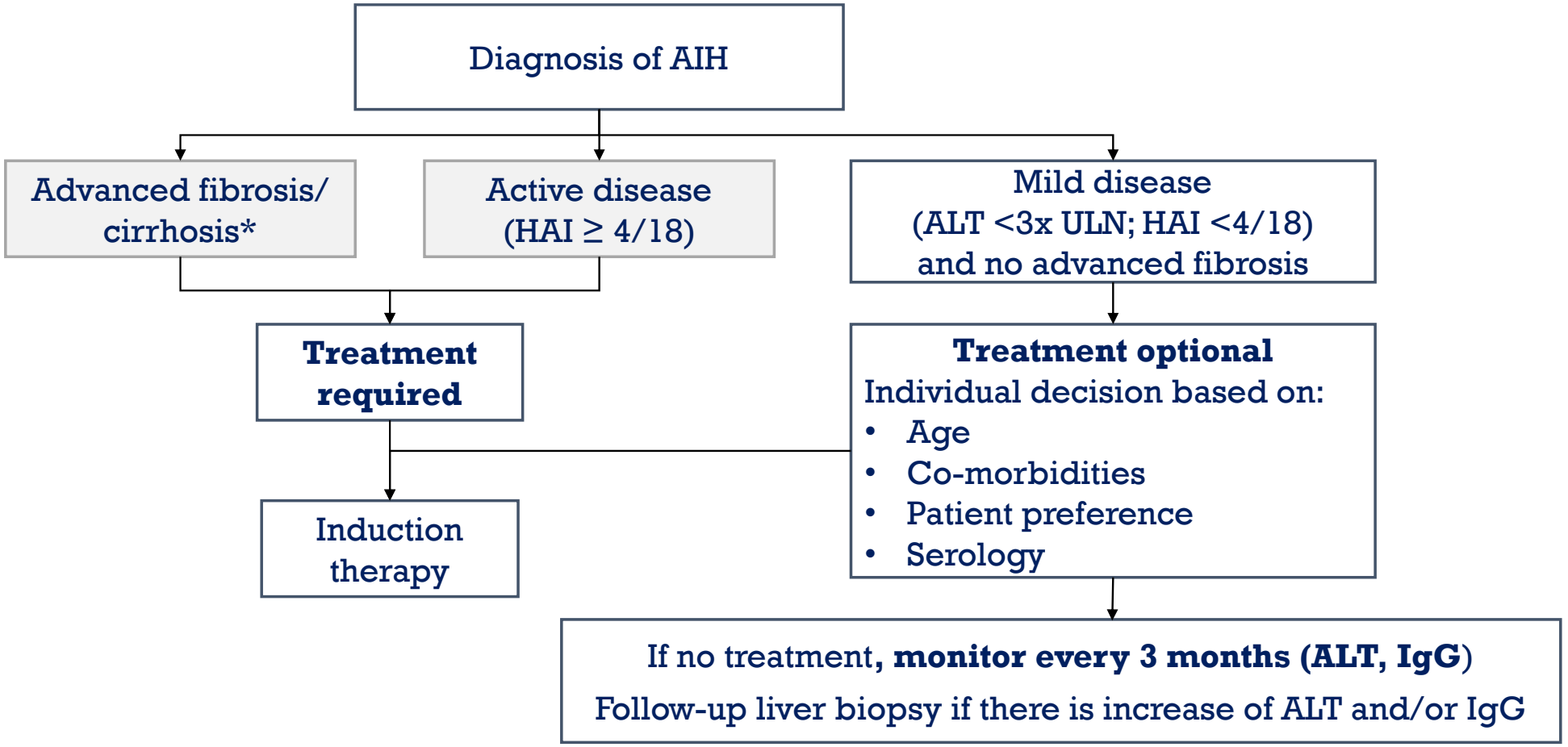
All children with a diagnosis of AIH **should undergo MRCP** to exclude primary (autoimmune) sclerosing cholangitis

Clinical assessment and therapeutic approach to patients with PBC or PSC and features of AIH



J Hepatol 2011 Feb;54(2):374-85

Therapeutic algorithm



J Hepatol 2015;63:971–1004

AASLD PRACTICE GUIDELINES

Diagnosis and Management of Autoimmune Hepatitis

< Indications for Immunosuppressive Treatment >

Absolute	Relative	None
• Serum AST>10 upper limit of normal • Serum AST>5 upper limit of normal & r-globulin greater than twice normal • Bridging necrosis or multiacinar necrosis on histologic exam	• Symptoms (fatigue, arthralgia, jaundice) • Serum AST or r-globulin less than absolute criteria • Interface hepatitis	• Asymptomatic with nl or near nl AST & r-globulin • Inactive cirrhosis or mild portal inflammation • Severe cytopenia (wbc < 2.5 X 10^9/L or PLT < 50 x 10^9/L)

Hepatology 2010 Jun;51(6):2193-213

❖Remission induction

AASLD 2010 AIH GUIDELINE

Time	Combination therapy		Steroids alone
	Prednisone	Azathioprine	Prednisone
Week 1	30	50	60
Week 2	20	50	40
Week 3	15	50	30
Week 4	10	50	30
Until clinical endpoint reached	10	50	20

Postmenopausal state
Osteoporosis
Brittle diabetes
Obesity
Acne
Emotional lability
Hypertension

Cytopenia
TPMT deficieny
Pregnancy
Malignancy
Short course (≤6 month)

Hepatology 2010 Jun;51(6):2193-213.

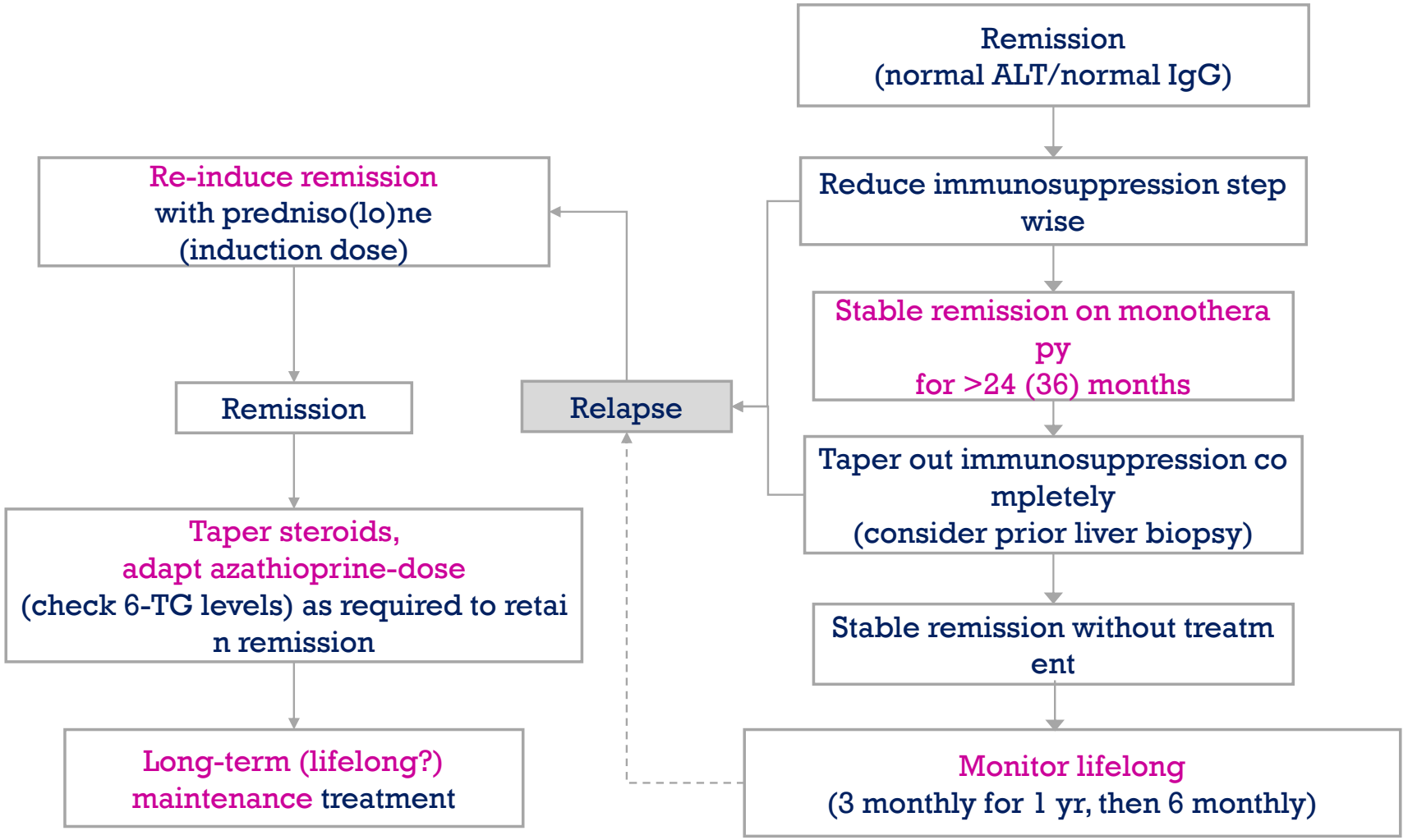
EASL 2015 AIH GUIDELINE

Treatment proposal for adult patients with AIH (e.g. 60 kg)

Week	Prednisolone (mg/day)	Azathioprine (mg/day)
1	60 (= 1 mg/kg body weight)	-
2	50	-
3	40	50
4	30	50
5	25	100*
6	20	100*
7 + 8	15	100*
8 + 9	12.5	100*
From week 10	10	100*

J Hepatol 2015;63:971–1004

❖Follow-up of patients with remission



J Hepatol 2015;63:971–1004

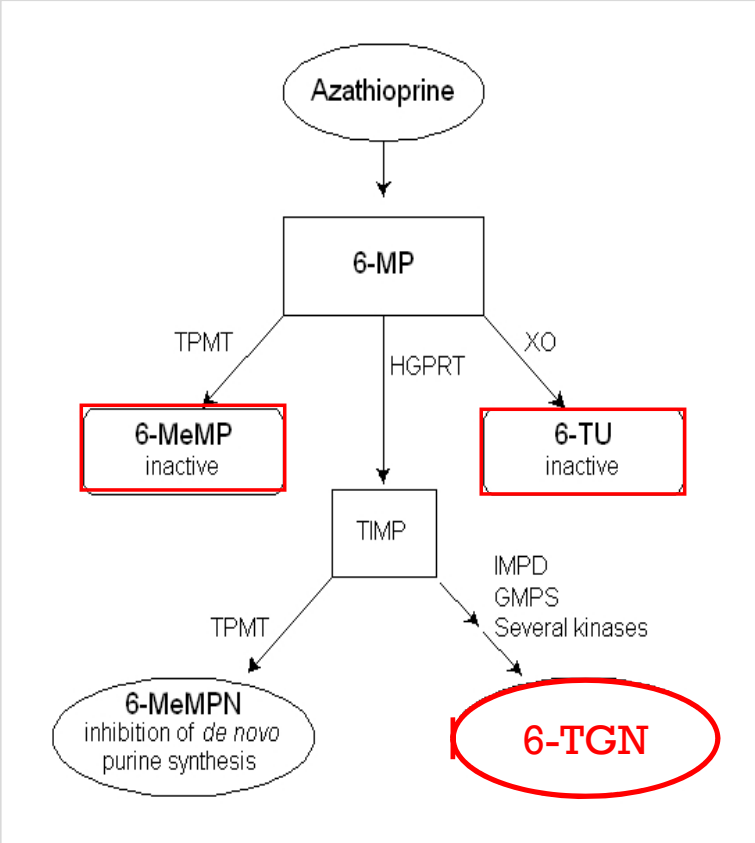
- **F/76**

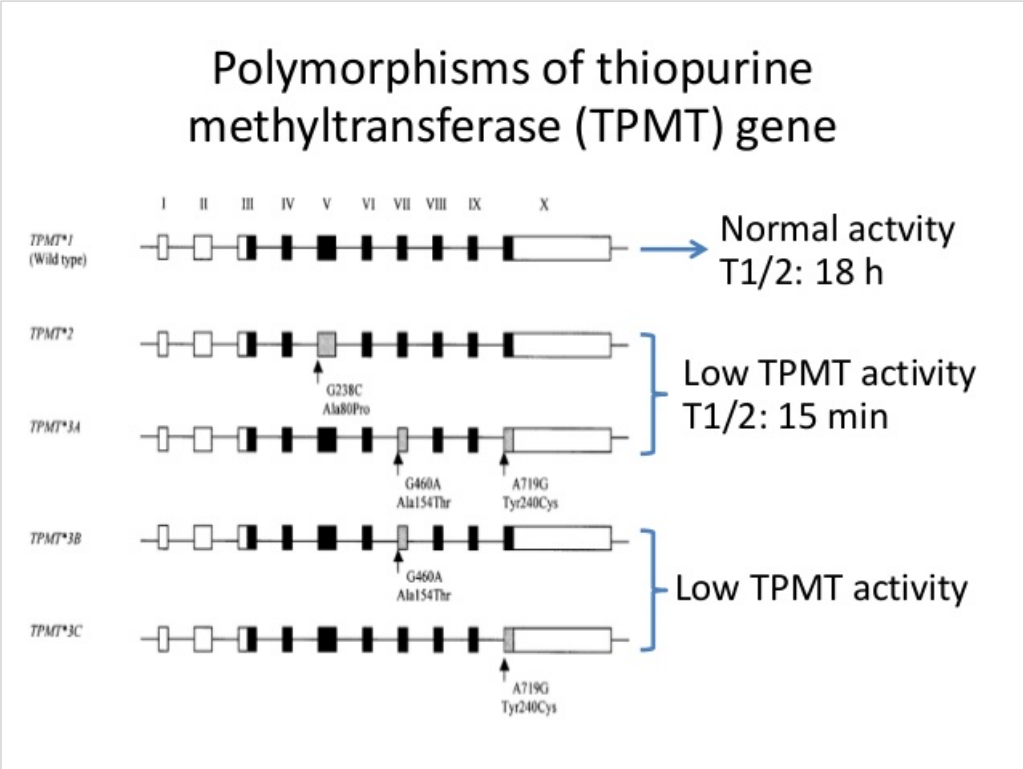
- **Thyroid ca로 op 예정 중 AST/ALT상승으로 방문**
- **AIHG score : 14 (probable) , simplified : 6 (probable)**

- **17.12.1) AZP/PRS start**
- **17.12.8) LFT – improving state**
- **17.12.24) fever , myalgia, coughing**

	2017/12/8	2017/12/25	2017/12/28	2018/01/05	2018/01/12
WBC	4370 (46%)	500 (7%) (eos:11%)	1090 (58%)	2060 (36.4%)	4370 (41.2%)
Hb	12.6	9.7	9.3	10.2	11.4
PLT	107K	41K	73K	121K	105K

Simplified representation of the thiopurine metabolism





< Thiopurine methyltransferase (TPMT) Major Polymorphism >

=[검사결과]

TPMT genotype	Enzyme activity
*1/*1(wild type)	Normal

[검사정보]
SPECIMEN: Genomic DNA isolated from peripheral blood leukocytes
ANALYZED GENE: TPMT on Chromosome 6p22.3
METHOD: PCR & Direct sequencing (Total 4 exons: exon 4,6,7,9)
REFERENCE SEQUENCE: NM_000367.2

[소견]
TPMT 유전형 중 한국인에서 보고된 바 있는 유전형(TPMT*3C, *6, *16, *32, *38)에 대한 직접염기서열 분석결과, 완려진 변이는 관찰되지 않았습니다.

❖AIH combined with other liver disease

- **F/52**
- **P.I : 상기환자 건강검진 초음파상 coarse echo로 2016.1.14 본원 방문**
- **Past Hx : Behcet disease**

- **CBC : 3600>-13.4-<216K**
- **AST/ALT 50/53, ALP/R-GTP 182/55, TB/DB 0.7/0.3**
- **US : early LC**

HBsAg/HBsAb/HCV-Ab(+/-/-)

AutoAb) IgG: 1962 mg/dl
ASMA (1: 100 dilution) : weakly positive

❖ SUMMARY

▪AIH is rare disease, but in most cases with proper treatment of immunosuppressive agent shows a high response rate.

▪ AIH is a clinical diagnosis.

▪ In countries with a high prevalence of viral hepatitis co-existence of AIH and viral hepatitis may exist In these cases the diagnosis of AIH may be overlooked and could remain untreated

▪The benefit to harm ratio should be considered before treatment

▪Treatment of AIH should be response guided and regimens should be individualized.

Thank you for your attention!!