Autoimmune Hepatitis :
Dutch Liver Week 20-06-2018

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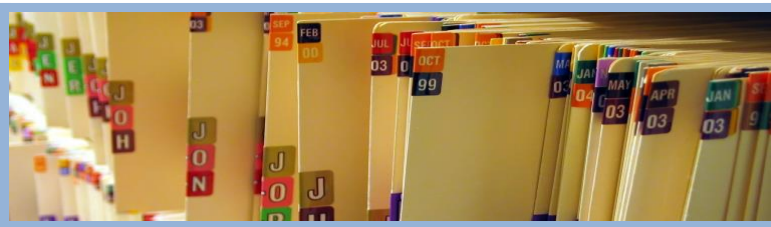
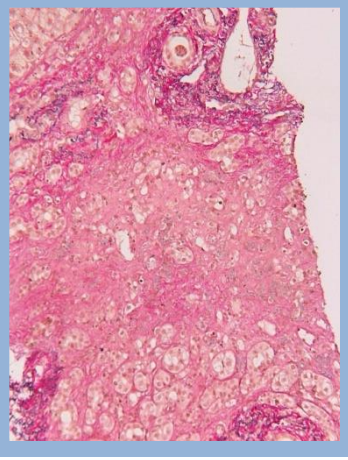




Amsterdam UMC
Universitair Medische Centra

Outline

- Case/questions
- Epidemiology
- Genetics
- Clinical spectrum
- Diagnosis
- Treatment
  - Difficult to treat patients
  - Drug intolerance and side effects
- Variant Syndroms
- Take Home

- Answers on questions

Case

A 32-year-old Caucasian woman presented to her primary care physician with a 3 month history of **anorexia, weight loss, fatigue and arthralgia.**

She was referred to us because laboratory testing had revealed **abnormal liver enzyme** values.

She was found to have **jaundiced sclerae**, but there were no signs of hepatosplenomegaly or bruises. Her weight was 65 kg.

Laboratory findings

ESR	12 mm/h
WBC	8.7
Hb	8.3
Trombocytes	237
Bilirubin	68 µmol/L (normal < 20)
ALT	691 IU/L (normal < 30)
AST	509 IU/L (normal < 45)
Alk Phos	110 IU/L (normal <100)
GGT	69 IU/L (normal <60)
INR	1.2
Albumin	38 g/L

Creatinin, Urea and electrolytes are normal

Viral, toxic and metabolic causes are negative

Case

- Which of the following test(s) is most appropriate?

A. Serum IgG and SMA
B. Serum IgM and AMA

Case

IgG	20 g/L (H)
ANA/SMA	1:160 / 1:640

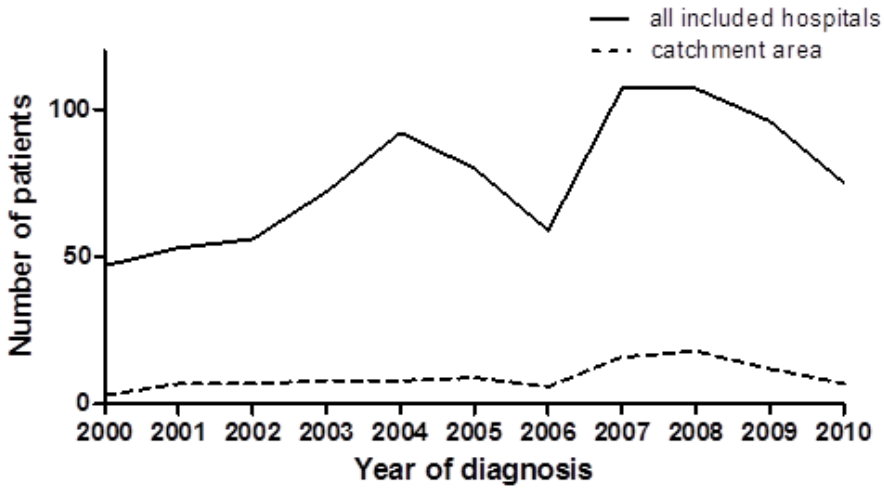
US: no abnormalities

Case

- What is the next step?

A. Fibroscan
B. Liverbiopsy

Autoimmune hepatitis in the Netherlands



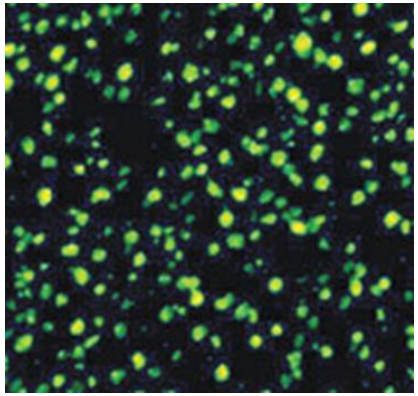
- 1313 AIH patients (78% female)
- Annual incidence: 1,1/100.000 (95% CI: 0.5-2)
- Prevalence: 18,3/100.000 (95% CI: 17.3-19.4)

- EASL 2015: prevalence 15-25/100.000

Van Gerven et al, Scand J Gastroenterol 2014;26:1104-1107

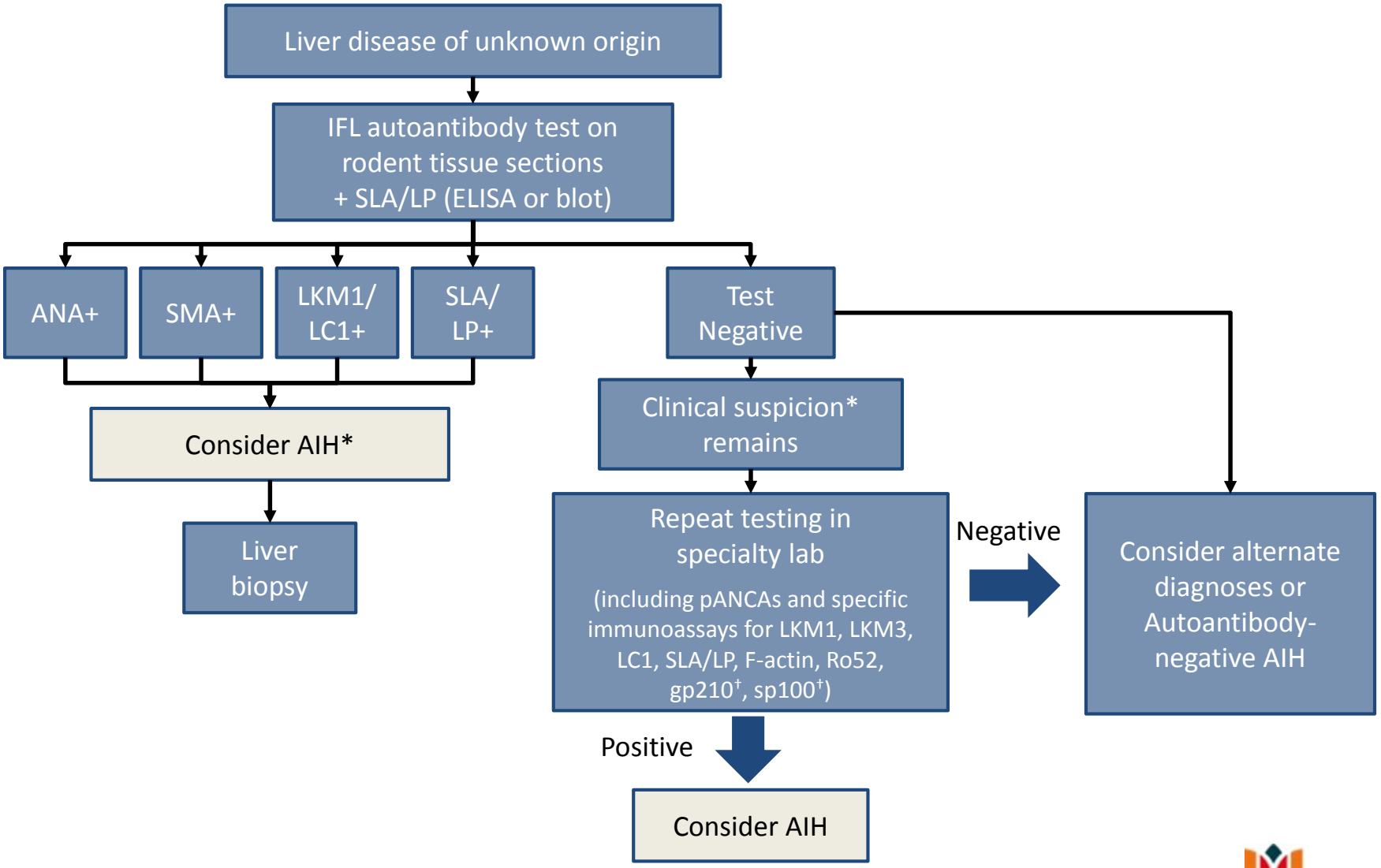
Autoimmune hepatitis - Diagnosis

- Myalgia, arthralgia, tired
- ALT and AST ↑ ↑
- IgG / immune globulins ↑ (85%)



- Exclusion of viral, metabolic and toxic causes
- Autoantibodies (75-90%)
- Compatible histology: prerequisite

Suggested diagnostic algorithm for AIH



*Test also for elevated IgG levels; †These antibodies are highly specific for PBC diagnosis

EASL CPG AIH. J Hepatol 2015;63:971–1004

Role of liver biopsy

- Essential to make or refute diagnosis
- Exclusion of other liver diseases
- Findings compatible rather then typical
- Information on prognosis and management
- Measures disease activity
- Not necessary to confirm the relapse

Differential Diagnosis of AIH

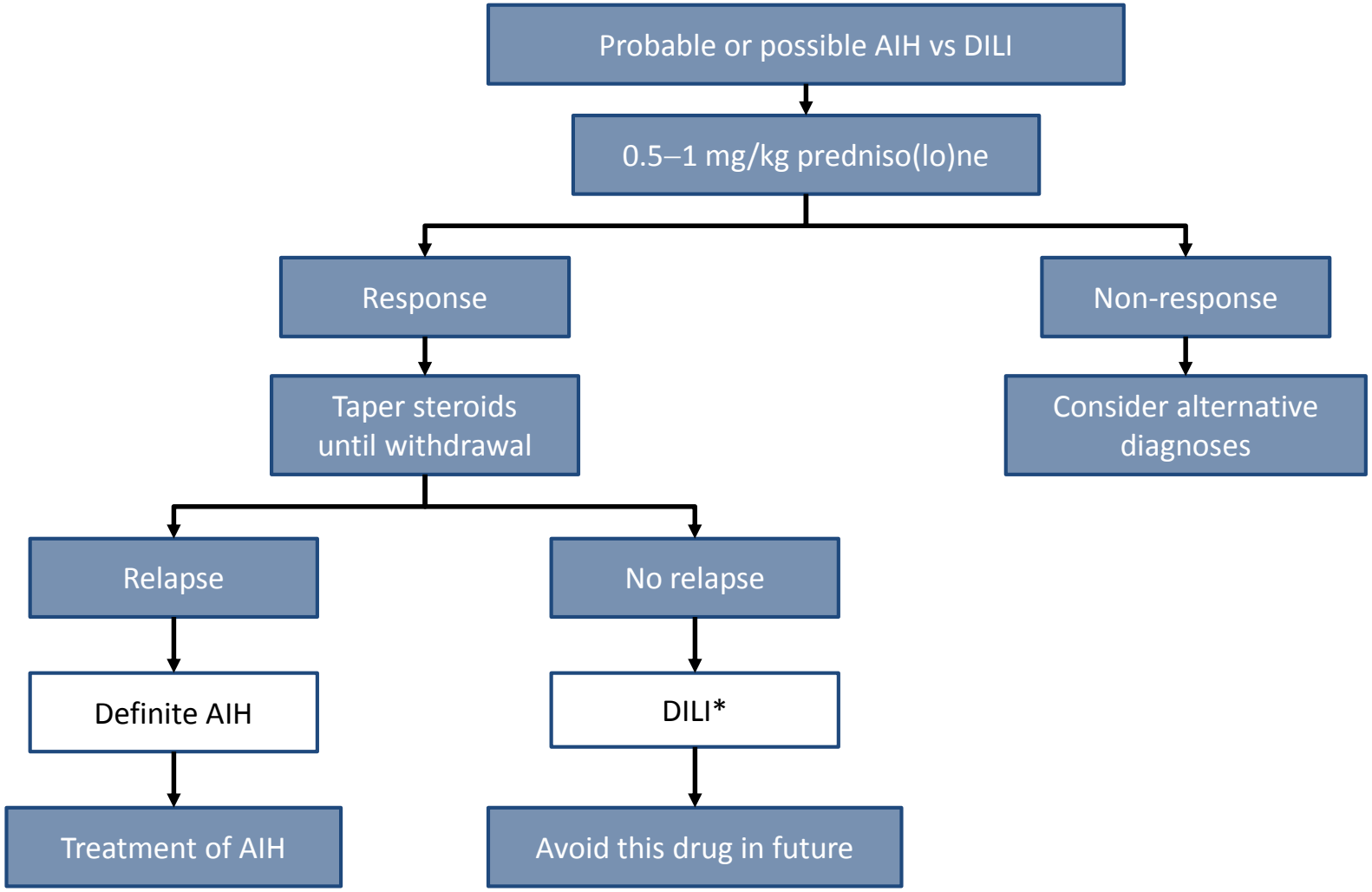
- **AIH should be considered in any patient with acute or chronic liver disease**
  - Particularly if hypergammaglobulinaemia is present and if the patient has features of other autoimmune diseases

Other autoimmune liver diseases	
• Primary biliary cirrhosis • Primary sclerosing cholangitis*	• IgG4-associated cholangitis
Chronic viral hepatitis	
• Chronic hepatitis B ± HDV	• Chronic hepatitis C
Other conditions	
• Cholangiopathy due to HIV infection • Alcoholic liver disease • Drug-induced liver injury • Granulomatous hepatitis • Haemochromatosis	• Non-alcoholic steatohepatitis • α1-antitrypsin deficiency • Wilson disease • Systemic lupus erythematosus • Coeliac disease

*Including small duct primary sclerosing cholangitis

EASL CPG AIH. J Hepatol 2015;63:971–1004

Suggested algorithm for AIH vs DILI



*Long-term follow-up is advised in order not to miss a late relapse of AIH (e.g. 6 monthly for 3 years)
EASL CPG AIH. J Hepatol 2015;63:971–1004

IAIHG criteria for diagnosis (1999)

- Typical features that inform a diagnosis of AIH

Definite AIH	Probable AIH
Normal α-1AT phenotype	Partial α-1AT deficiency
Normal ceruloplasmin level	Non-diagnostic ceruloplasmin/copper levels
Normal iron and ferritin levels	Non-diagnostic iron and/or ferritin changes
No active hepatitis A/B/C infection	No active hepatitis A/B/C infection
ANA, SMA anti-LKM1 >1:80, in adults and >1:20 in children	ANA, SMA, anti-LKM1 >1:40 in adults
AMA negative	Other autoantibodies
Liver histology • Interface hepatitis moderate to severe • No biliary lesions, granulomas or prominent changes suggestive of another disease	Liver histology • Interface hepatitis moderate to severe • No biliary lesions, granulomas or prominent changes suggestive of another disease

Complex as a clinical tool
Fails to distinguish AIH from cholestatic syndromes

Alvarez F, et al. J Hepatol 1999;31:929–38; EASL CPG AIH. J Hepatol 2015;63:971–1004

IAIHG simplified scoring system (2008)

- Diagnostic criteria for routine clinical use

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

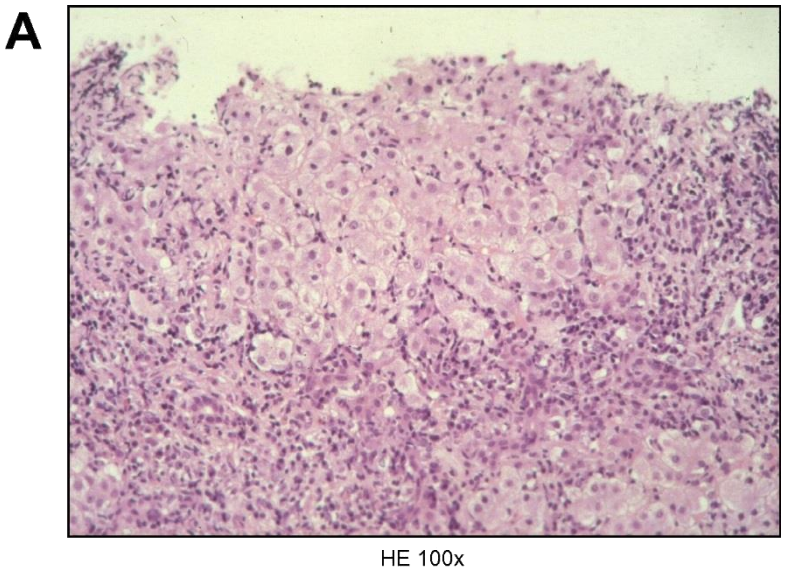
Hennes EM, et al. Hepatology 2008;48:169–76; EASL CPG AIH. J Hepatol 2015;63:971–1004

Typical histopathology of AIH

A. Typical histopathology of AIH with portal/periportal predominance of necroinflammatory lesions and broad interface hepatitis with lymfocytic-plasmacellulair infiltrates

B. Emperipolesis with a lymphocyte in the cytoplasm of a damaged hepatocyte

C. Typical rosetting of hepatocytes in the area of interface hepatitis



Manns MP, et al. J Hepatol 2015;62:S100–11
Histopathology pictures were provided by Hans Peter Dienes, University of Vienna, Austria

ISHAK modification: hepatic activity index (HAI)

Item	Score
Periportal or periseptal interface hepatitis (piecemeal necrosis)	0-4
Confluent necrosis	0-6
Focal (spotty) lytic necrosis, apoptosis and focal inflammation	0-4
Portal inflammation	0-4

Clinical Relevance

Decisions on start & stop therapy in AIH requires a liver biopsy

- Start therapy if HAI ≥ 4
- Stop therapy (if desired) HAI < 3

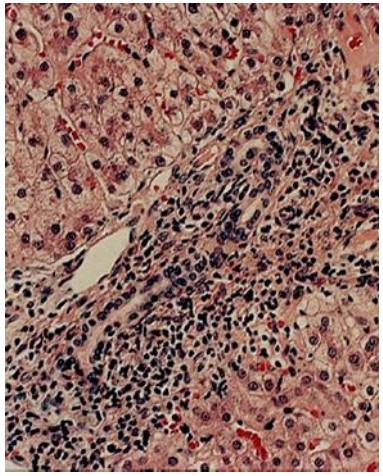
Modern Pathology 2007:20, S3-14 EASL CPG 2015

AIH Classification: autoantibodies based

AIH type	Autoantibodies	Specifics
1	ANA; SMA	-80% of cases -adults -slow onset
2	LKM1 LKM3; LC1	-20% of cases -pediatric -fulminant cases
3	SLA/LP	similar to type 1 -more relapse -more difficult to treat

Presentation (1)

- Any age, peaks puberty and 40-60 years
- All ethnic groups
- Asymptomatic – acute severe or even fulminant
- 2/3 insidious onset: fatigue, nausea, weight loss, malaise, amenorrhoea, RU abdominal pain, arthralgia, skinrash, temperature etc)
- 25% acute hepatitis: acute on chronic or true acute, auto-ab can be absent
- 1/3 have cirrhosis at presentation, 1/2 of children

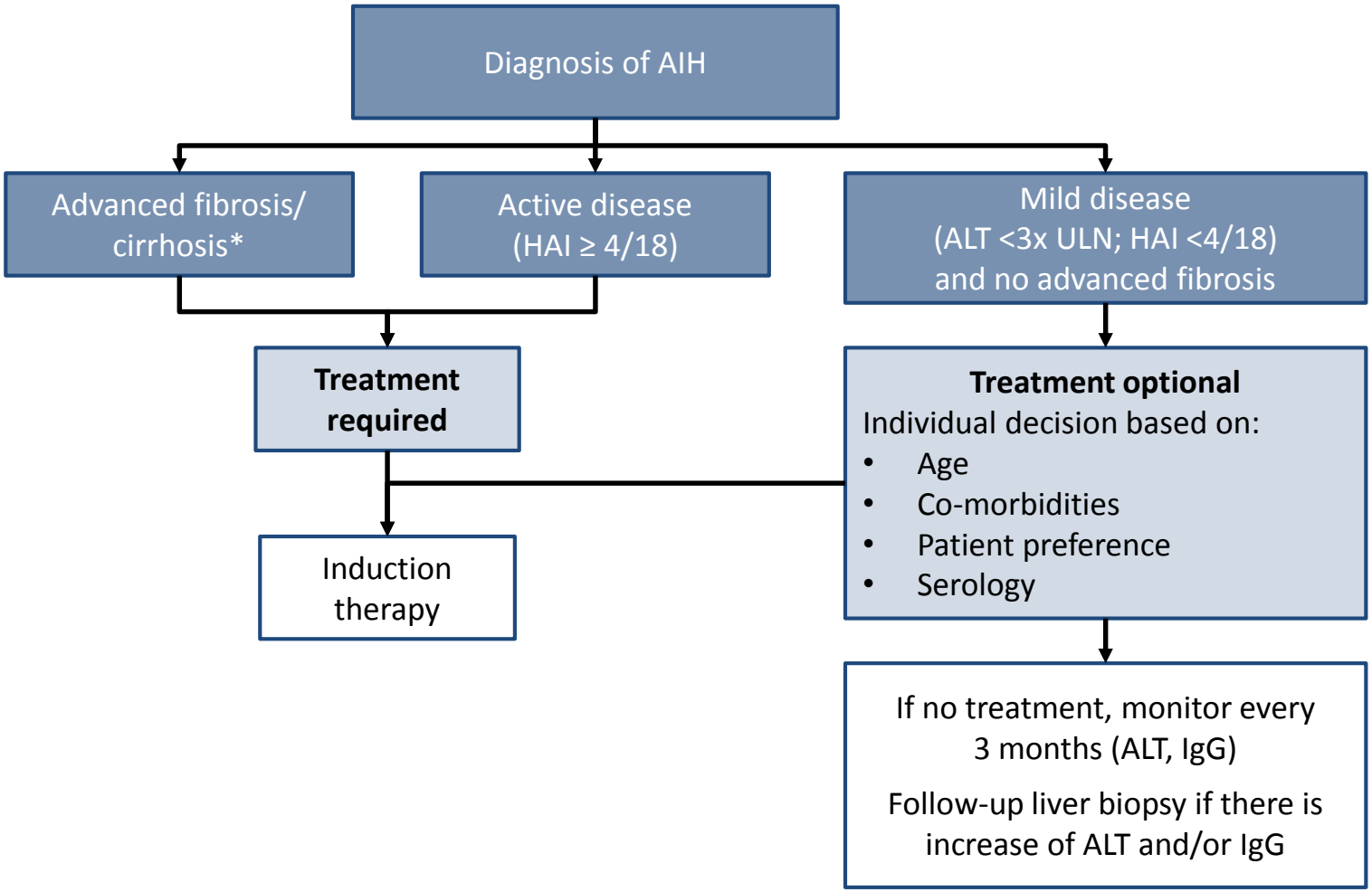


30-50%: other autoimmune phenomena

Treatment

- Should I treat AIH, if so when?
- How should I treat?
- What should I treat?
- Can I stop?

Therapeutic algorithm



*Treatment probably no longer indicated in decompensated, burned-out cirrhosis, unless high inflammatory score on liver biopsy

EASL CPG AIH. J Hepatol 2015;63:971–1004

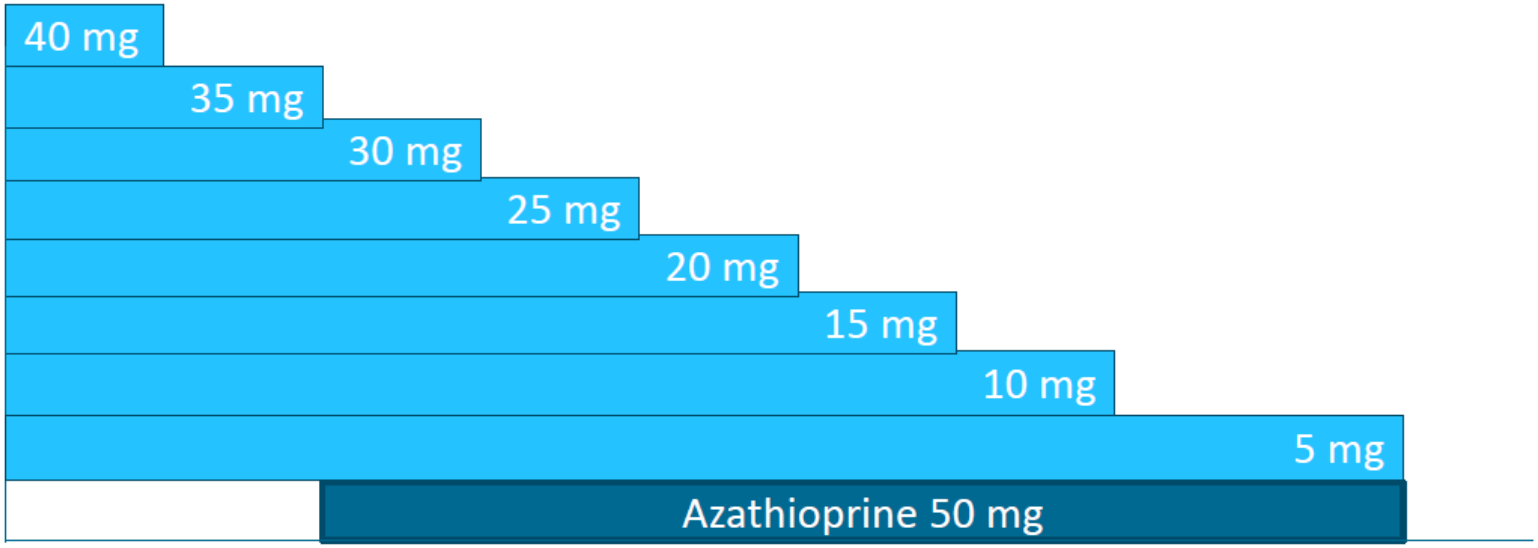
How to start treatment in AIH

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

European Association for the Study of the Liver*

Example patient 75 kg

Prednisone: 0.5-1 mg/kg/day & Azathioprine 50 mg/day



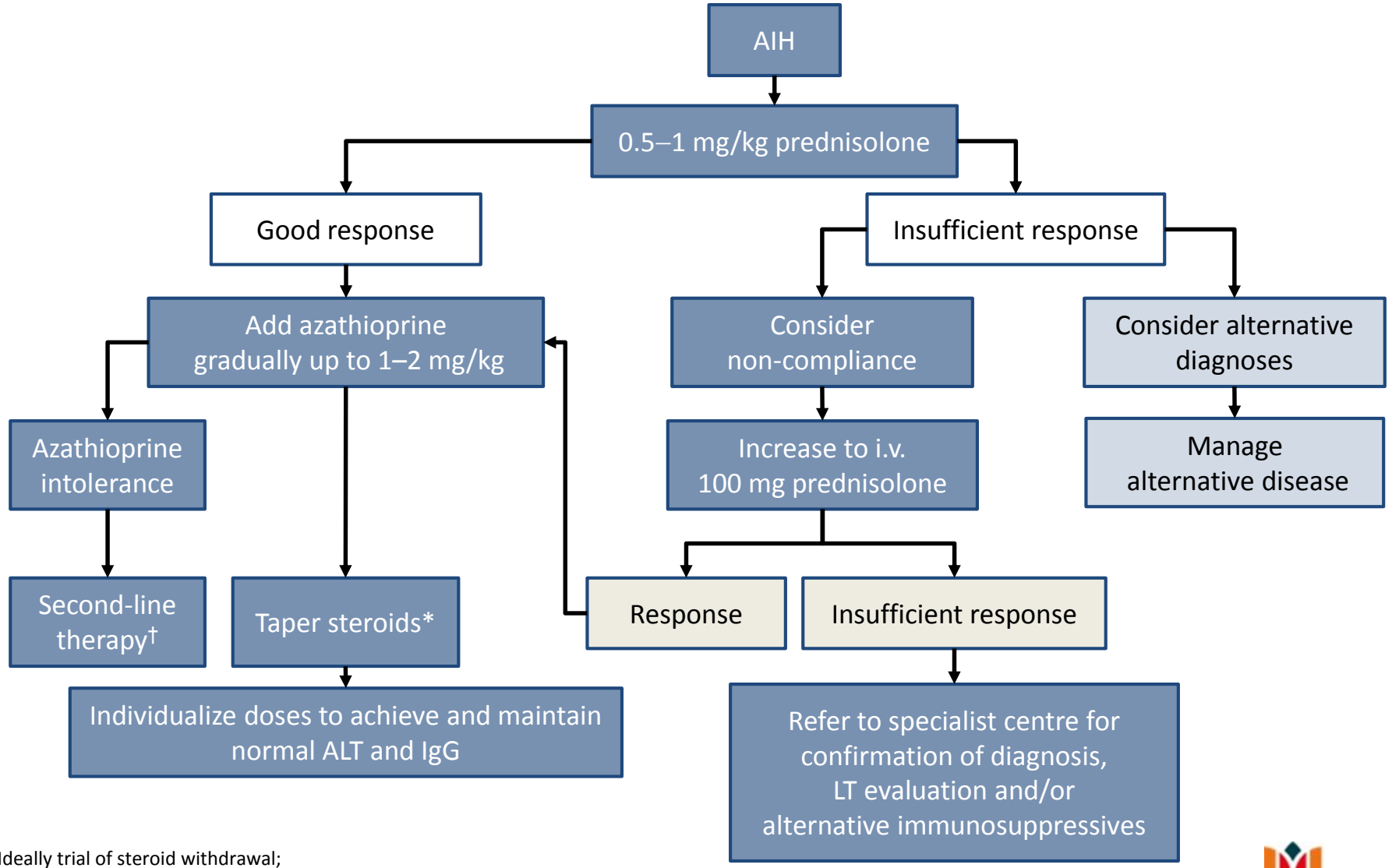
Measure

Efficacy: ALT & IgG as outcome measures

Safety: kreatinine, lipase, leukocytes

CPG AIH J Hep 2015

Therapeutic strategy



*Ideally trial of steroid withdrawal;
†Usually MMF

EASL CPG AIH. J Hepatol 2015;63:971–1004

Treatment duration and response

- Aim: complete normalization of aminotransferases and IgG levels
  - Persisting elevations of aminotransferases associated with:
    - Relapse after treatment withdrawal
    - Activity on liver biopsy
    - Progression to cirrhosis
    - Poor outcome
- Biochemical remission = normalization of IgG and ALT
- Histological remission = normal histology or minimal hepatitis (HAI ≤ 4)
- Immunosuppressive treatment at least 3 years and 2 years following complete normalization of ALT and IgG
- Without biochemical remission treatment should not be discontinued.
- If > 2 years in biochemical remission consider liver biopsy
  If HAI > 3 do not stop

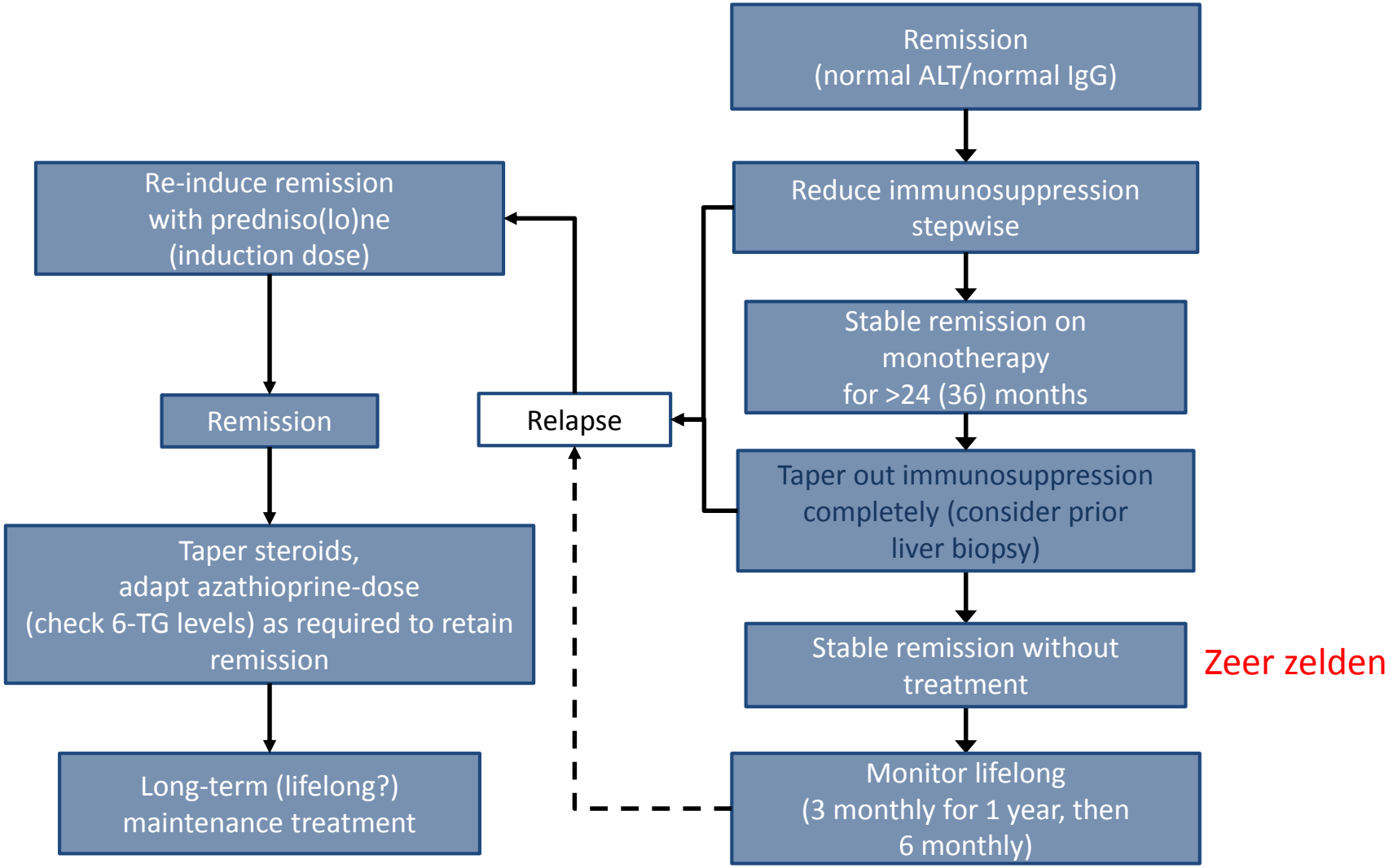
*Statement numbers: 30–32;
†Histological resolution of disease typically lags behind reaching the biochemical endpoint
EASL CPG AIH. J Hepatol 2015;63:971–1004

Suboptimal response

- Primary non-response to immunosuppressive treatment is experienced in only a very small proportion of patients
  - Carefully reconsider diagnosis
  - Re-evaluate adherence to treatment
  - Increase dosage prednisolone and azathioprine, or alternative medication
  - Lack of improvement in acute severe AIH (iv cortico's > 1mg/kg) within 7 days: consider emergency liver transplantation

*Statement numbers: 27–29
EASL CPG AIH. J Hepatol 2015;63:971–1004

Follow-up of patients with remission



EASL CPG AIH. J Hepatol 2015;63:971–1004

Identification problematic patients

MELD score > 11 on presentation

No improvement MELD after 7 days treatment in icteric patients

Multilobulair necrosis, hyperbilirubinaemia,
no improvement or even deterioration in 2 weeks

Anti-SLA of LKM

AASLD practice guidelines 2010

Maintenance treatment

Respons guided and individualized strategy

- Azathioprine 1,5-2 mg/kg/day

  or

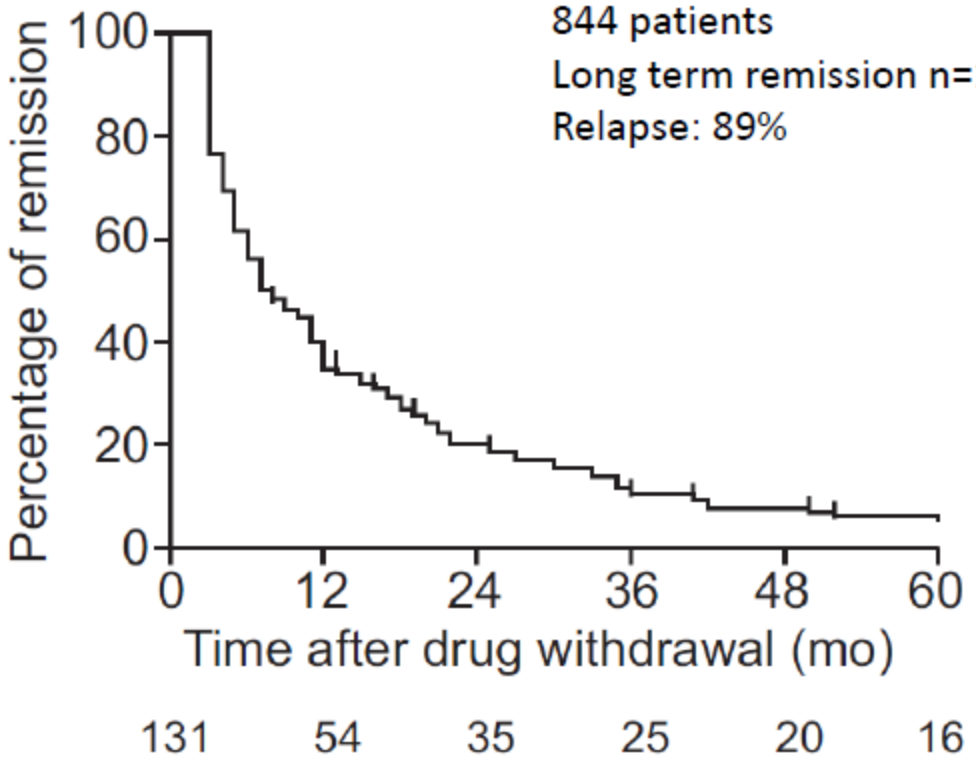
- Lowest effective dose prednisolone ≤ 10 mg

  or

- Prednisolone ≤ 10 mg or budesonide 3 mg plus Azathioprine

AASLD practice guidelines 2010

Treatment withdrawal and relapse



844 patients
Long term remission n=131 (nl ALT for 2 yrs)
Relapse: 89%

Relapse is almost universal on withdrawal of immunosuppressive therapy

*All patients had been in remission for at least 2 years prior to drug withdrawal
Van Gerven et al. J Hepatol 2013;58:141–7
EASL CPG AIH. J Hepatol 2015;63:971–1004

TPMT deficiency

- TPMT is an enzyme involved in the metabolism of azathioprine
  - TPMT deficiency can result in increased toxicity of azathioprine
- TPMT testing cannot always identify those likely to experience toxicity
  - Deficiency associated with various alleles
  - Alternative pathways of metabolism
  - Variable penetrance
  - Possible substrate induction of TPMT activity
- **Potential serious consequences make TPMT testing valid prior to azathioprine**
- In patients with TPMT deficiency consider
  - Prednisolone monotherapy
  - Lower dose prednisolone + MMF
- Close monitoring for toxicity (blood counts) of all patients started on azathioprine is mandatory

Guideline statements*	Grade of recommendation
TGN measurements may help to guide azathioprine dosage and to detect possible non-adherence. Undetectable TGN levels may be due to altered metabolism or non-adherence. High TGN levels may suggest toxicity	II-2

*Statement number: 38

EASL CPG AIH. J Hepatol 2015;63:971–1004

Drug intolerance and adverse effects

Prednisone or prednisolone adverse events are common in AIH
up to 80% after 2 years, treatment discontinuation in 15%

Azathioprine adverse effect are less common
up to 25% pts after 2 years, with treatment discontinuation in 10%

Without cirrhosis budesonide plus azathioprine maybe used as alternative therapy
Long term data on budesonide are lacking
Severe steroid side effects consider switch to budesonide

Aza intolerant: MMF second line

Trial of 6-TG in pts intolerant to azathioprine is an option

EASL CPG AIH. J Hepatol 2015;63:971–1004

Alternative therapies to corticosteroids and azathioprine

Medication	Dose	Major side effects
Cyclosporine A	3-5 mg/kg KG/qd	Hypertension Renal insufficiency
Tacrolimus	3-5 mg bid	Hypertension Renal insufficiency Diabetes Polyneuropathy
Mycophenolate mofetil	750-1000 mg bid	GI-symptoms Diarrhoea, Leukopaenia
Anti-TNF mAb (Infliximab)	5 mg/kg body weight Every 2-8 weeks	Infections Induction of immune mediated liver injury
Anti-CD20 mAb (Rituximab)	2x1000 mg infusions Day 1 and 15	Reactivation of infections, e.g., hepatits B

Qd, once daily; bid, two times per day.

Michael P. Manns , Ansgar W. Lohse , Diego Vergani. **Autoimmune hepatitis – Update 2015** Journal of Hepatology, Volume 62, Issue 1, Supplement, 2015, S100 - S111

Variant syndromes with AIH

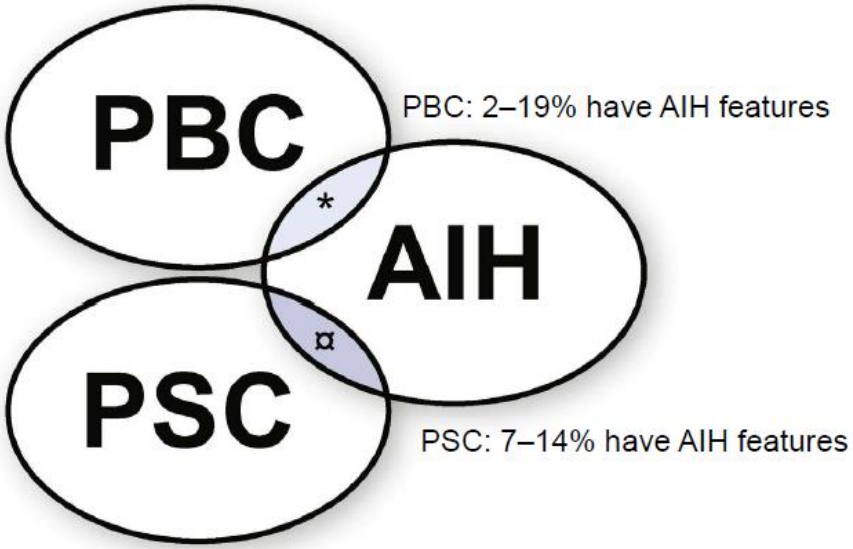


Table 2. Selected studies of PBC–AIH and PSC–AIH overlap conditions.

Criterium for diagnosis of overlap condition	Reference	No. of patients	Proportion (%) of patients with overlapping features
At least 2 of 3 criteria of PBC and AIH	[61] [63]	130 - 331	4.8 – 9.2% PBC-AIH
Revised IAIHG criteria applied to PBC patients	[23] [44] [66] [70] [71]	137 - 368	2.1 – 19% PBC-AIH
Revised IAIHG criteria applied to PSC patients	[7]* [70] [82] [83]	113 - 221	7.4 – 14% PSC-AIH

* Presenting the results of application of the revised IAIHG scoring system to the group of PSC patients previously scored [52] according to the original IAIHG system.

J Hepat 2011: 54, 3740385

Variant syndromes

- Randomized controlled trials are lacking, but also impractical
  - Low prevalence of the variant syndromes
  - Lack of universal definitions

Guideline statements*	Grade of recommendation
In **AIH patients with features of PBC** (“AIH-PBC variant syndrome”), combined therapy with **UDCA and immunosuppressants is recommended**	III
In **AIH patients with PSC features** (“AIH-PSC variant syndrome”) addition of UDCA to **immunosuppressant** can be **considered**	III
In patients with **dominant AIH features**, an **alternative** approach is to start with **immunosuppressants only and then add UDCA** if response is insufficient	III

*Statement number: 50

EASL CPG AIH. J Hepatol 2015;63:971–1004

Special patient populations: Osteopenia/osteoporosis and vaccination

- Patients receiving several courses of high dose steroids have a substantially increased risk of fracture
  Measurement of bone density, vitamin D and adequate calcium intake

- Viral hepatitis and its management can complicate AIH
  All patients with AIH should receive **hepatitis A and B vaccination and yearly influenza vaccination**

EASL CPG AIH. J Hepatol 2015;63:971–1004

Take home

Acute or chronic hepatitis: think of AIH

For diagnosis liver biopsy

Clinical and biochemical remission in most patients with prednisone and azathioprine

Azathioprine intolerance: MMF also option

Budesonide might be an alternative for patients without cirrhosis

Questions or suggestions?
www.autoimmuunhepatitis.nl

Take home

Difficult to treat and/or no remission possible: center of expertise

Variant Syndrome AIH with PSC or PBC: treat both

Relapse is almost universal on withdrawal of immunosuppressive therapy

Subgroup of patients that can stop treatment finally? STOP study

Questions or suggestions?
www.autoimmuunhepatitis.nl

Case

- Which of the following test(s) is most appropriate?

A. Serum IgG and SMA

B. Serum IgM and AMA

Case

IgG	20 g/L (H)
ANA/SMA	1:160 / 1:640
Hepatitis A/B/C/E	negative

US: no abnormalities

What is the next step?

Case

- What is the next step?

A. Fibroscan

B. Liverbiopsy

Dutch studies

Ongoing:

- Thiopurine-metabolism
- Camaro study: cellsept vs azathioprine in remssion induction
- STOP study
- Steroid related side effects
- And more to come

In press:

- Low or high prednison for induction
- 6TG
- Mortality in AIH

NEDERLANDSE WERKGROEP AUTO-IMMUUN HEPATITIS