EASL guideline:
Autoimmune hepatitis

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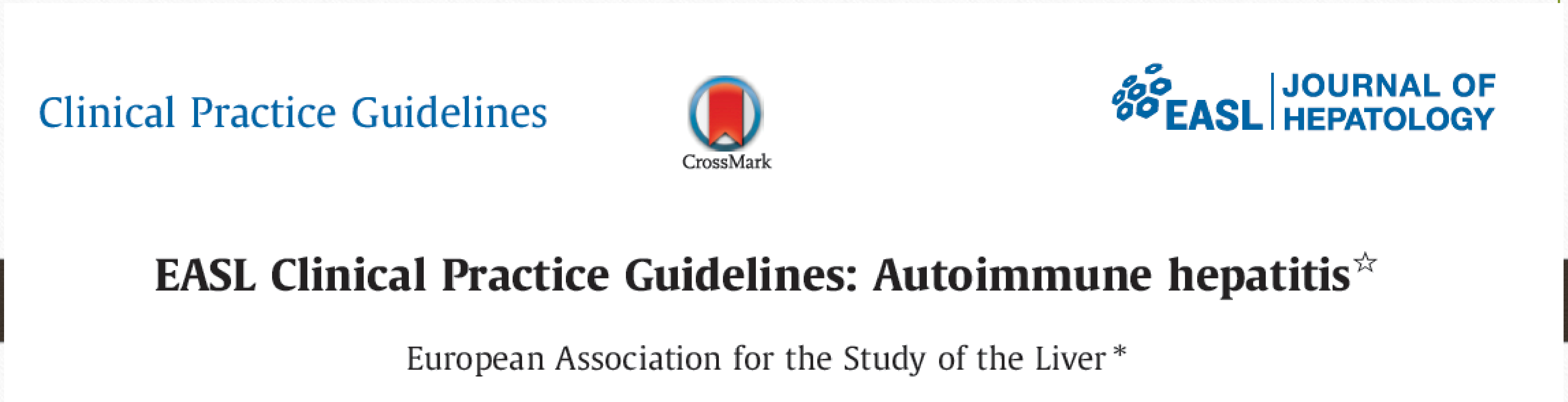

Clinical Practice Guidelines

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EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

European Association for the Study of the Liver *

Autoimmune hepatitis (AIH) was the first liver disease for which
an effective therapeutic intervention, corticosteroid treatment,
was convincingly demonstrated in controlled clinical trials.

However, 50 years later AIH still remains a major diagnostic and therapeutic challenge. There are two major reasons for this apparent contradiction: Firstly, AIH is a relatively rare disease. Secondly, AIH is a very heterogeneous disease

The wide
heterogeneity of affected patients and clinical manifestations of the disease limits both diagnostic and further therapeutic studies

AIH’s age spectrum is extremely wide, it can affect small infants and can manifest for the first time in octogenarians. AIH can run a very mild subclinical course or be very acute, rarely leading to fulminant hepatic failure

AIH sometimes demonstrates quite
dramatic disease fluctuations with periods of apparent spontaneous remissions, acute flares and/or smouldering disease

AIH

can be associated with a number of other hepatic conditions, in particular the cholestatic liver diseases; primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), but also with drug-induced liver injury (DILI), alcoholic or non-alcoholic steatohepatitis (NASH) or viral hepatitis

Each condition provides
special diagnostic and therapeutic challenges. Despite these challenges
and complexities, diagnosis and treatment of AIH has seen

striking progress, and now patients in specialised centres have an excellent prognosis, both in respect to survival and to quality of life

The aim of the present Clinical Practice Guideline (CPG) is to provide guidance to hepatologists and general physicians in the diagnosis and treatment of AIH in order to improve care for affected patients

In view of the limited data from large controlled studies and trials, many recommendations are based on expert consensus

AIH is an non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens (HLA) DR3 or DR4, interface hepatitis on liver histology, and a favourable response to immunosuppression [2–5]. The disease, if untreated, often leads to cirrhosis, liver failure and death.

AIH is considered relatively rare, as its prevalence ranges from
16 to 18 cases per 100,000 inhabitants in Europe [6–11]. Until
recently, the incidence and prevalence of AIH on a populationbased
level was assessed in only two studies

Interestingly
however, higher prevalence rates have been reported in areas with quite stable populations. For instance, prevalence rates of 42.9 cases per 100,000 and 24.5 cases per 100,000 inhabitants have been reported in Alaska natives [12] and New Zealand [9], respectively.

1. Prevalence of AIH ranges from 15 to 25 cases per 100,000 inhabitants in Europe and is increasing in both women and men **(II-2)**
AIH can affect all populations and all age groups **(II-2)**

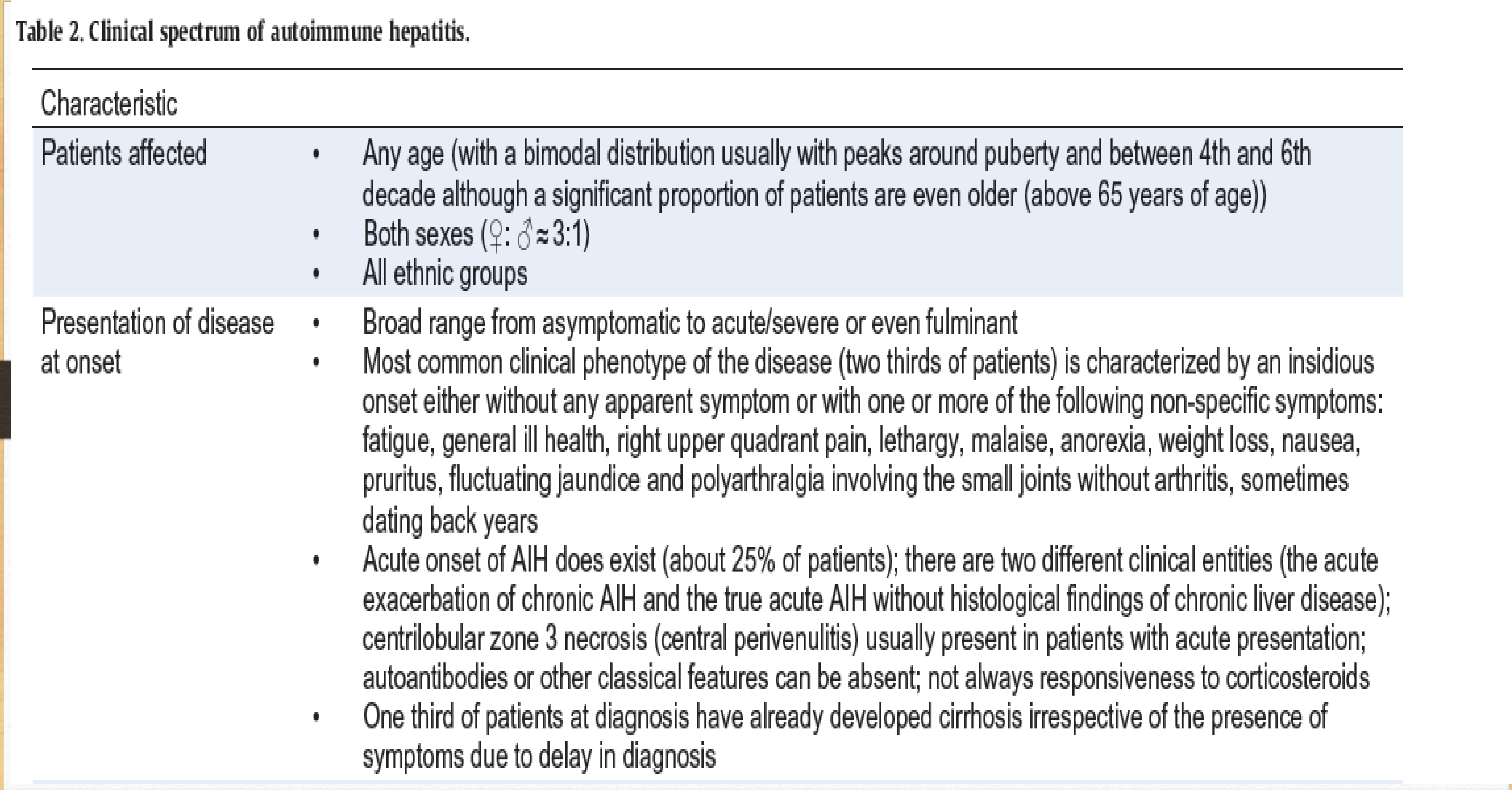
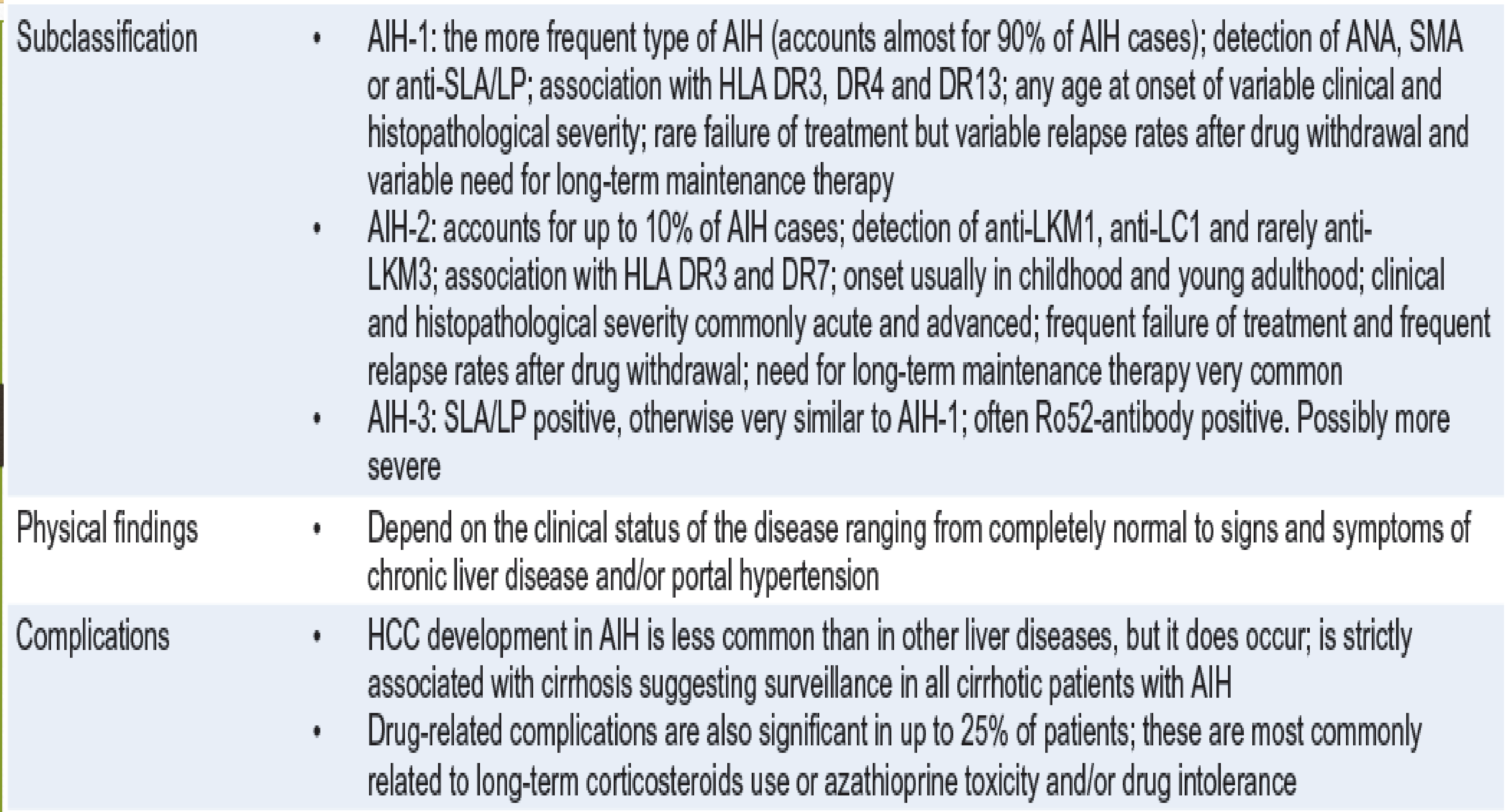


Table 2. Clinical spectrum of autoimmune hepatitis.

Characteristic	
Patients affected	• Any age (with a bimodal distribution usually with peaks around puberty and between 4th and 6th decade although a significant proportion of patients are even older (above 65 years of age)) • Both sexes (♀: ♂≈3:1) • All ethnic groups
Presentation of disease at onset	• Broad range from asymptomatic to acute/severe or even fulminant • Most common clinical phenotype of the disease (two thirds of patients) is characterized by an insidious onset either without any apparent symptom or with one or more of the following non-specific symptoms: fatigue, general ill health, right upper quadrant pain, lethargy, malaise, anorexia, weight loss, nausea, pruritus, fluctuating jaundice and polyarthralgia involving the small joints without arthritis, sometimes dating back years • Acute onset of AIH does exist (about 25% of patients); there are two different clinical entities (the acute exacerbation of chronic AIH and the true acute AIH without histological findings of chronic liver disease); centrilobular zone 3 necrosis (central perivenulitis) usually present in patients with acute presentation; autoantibodies or other classical features can be absent; not always responsiveness to corticosteroids • One third of patients at diagnosis have already developed cirrhosis irrespective of the presence of symptoms due to delay in diagnosis



Subclassification	• AIH-1: the more frequent type of AIH (accounts almost for 90% of AIH cases); detection of ANA, SMA or anti-SLA/LP; association with HLA DR3, DR4 and DR13; any age at onset of variable clinical and histopathological severity; rare failure of treatment but variable relapse rates after drug withdrawal and variable need for long-term maintenance therapy • AIH-2: accounts for up to 10% of AIH cases; detection of anti-LKM1, anti-LC1 and rarely anti-LKM3; association with HLA DR3 and DR7; onset usually in childhood and young adulthood; clinical and histopathological severity commonly acute and advanced; frequent failure of treatment and frequent relapse rates after drug withdrawal; need for long-term maintenance therapy very common • AIH-3: SLA/LP positive, otherwise very similar to AIH-1; often Ro52-antibody positive. Possibly more severe
Physical findings	• Depend on the clinical status of the disease ranging from completely normal to signs and symptoms of chronic liver disease and/or portal hypertension
Complications	• HCC development in AIH is less common than in other liver diseases, but it does occur; is strictly associated with cirrhosis suggesting surveillance in all cirrhotic patients with AIH • Drug-related complications are also significant in up to 25% of patients; these are most commonly related to long-term corticosteroids use or azathioprine toxicity and/or drug intolerance

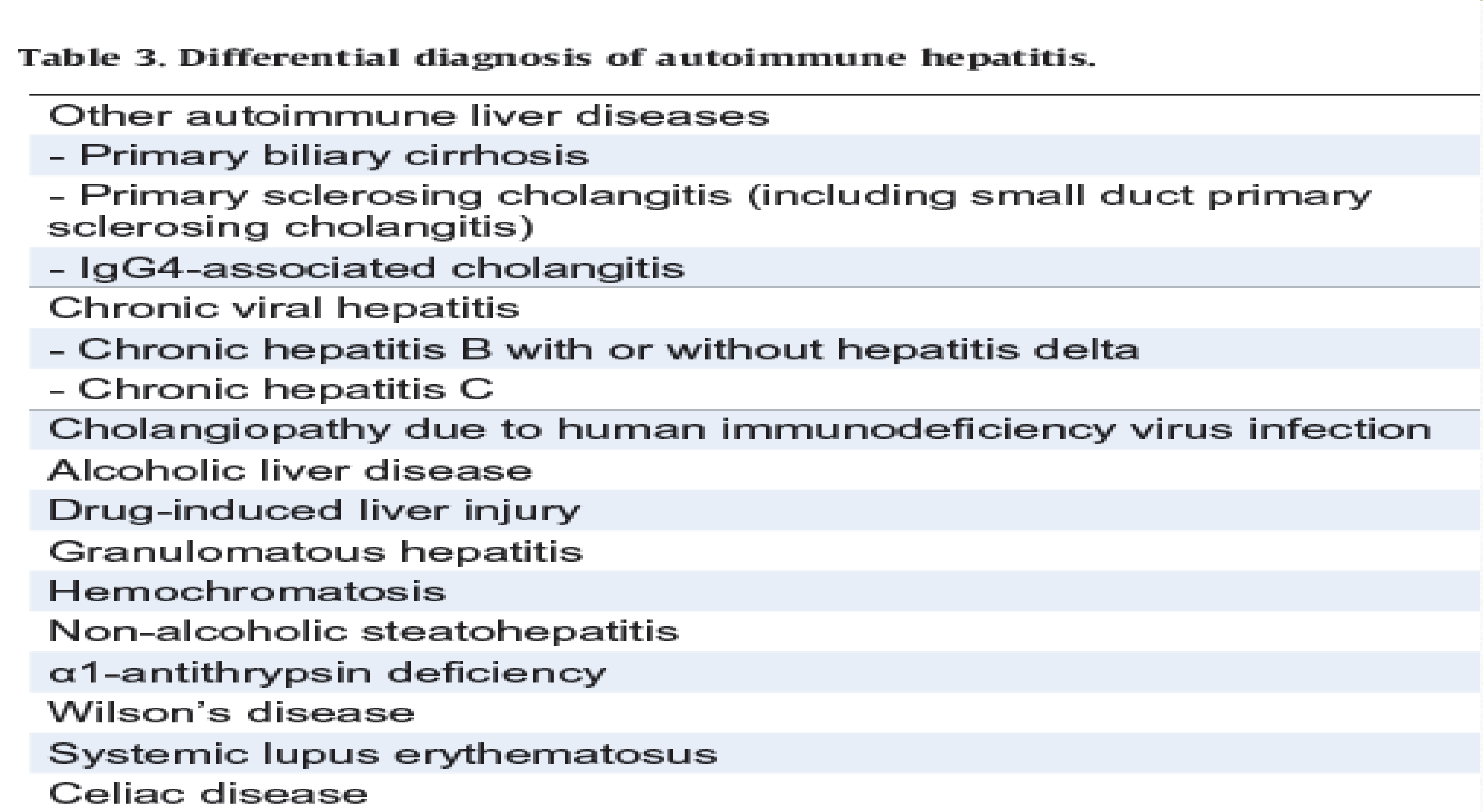


Table 3. Differential diagnosis of autoimmune hepatitis.

- Other autoimmune liver diseases
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis (including small duct primary sclerosing cholangitis)
  - IgG4-associated cholangitis
- Chronic viral hepatitis
  - Chronic hepatitis B with or without hepatitis delta
  - Chronic hepatitis C
- Cholangiopathy due to human immunodeficiency virus infection
- Alcoholic liver disease
- Drug-induced liver injury
- Granulomatous hepatitis
- Hemochromatosis
- Non-alcoholic steatohepatitis
- α1-antithrypsin deficiency
- Wilson’s disease
- Systemic lupus erythematosus
- Celiac disease

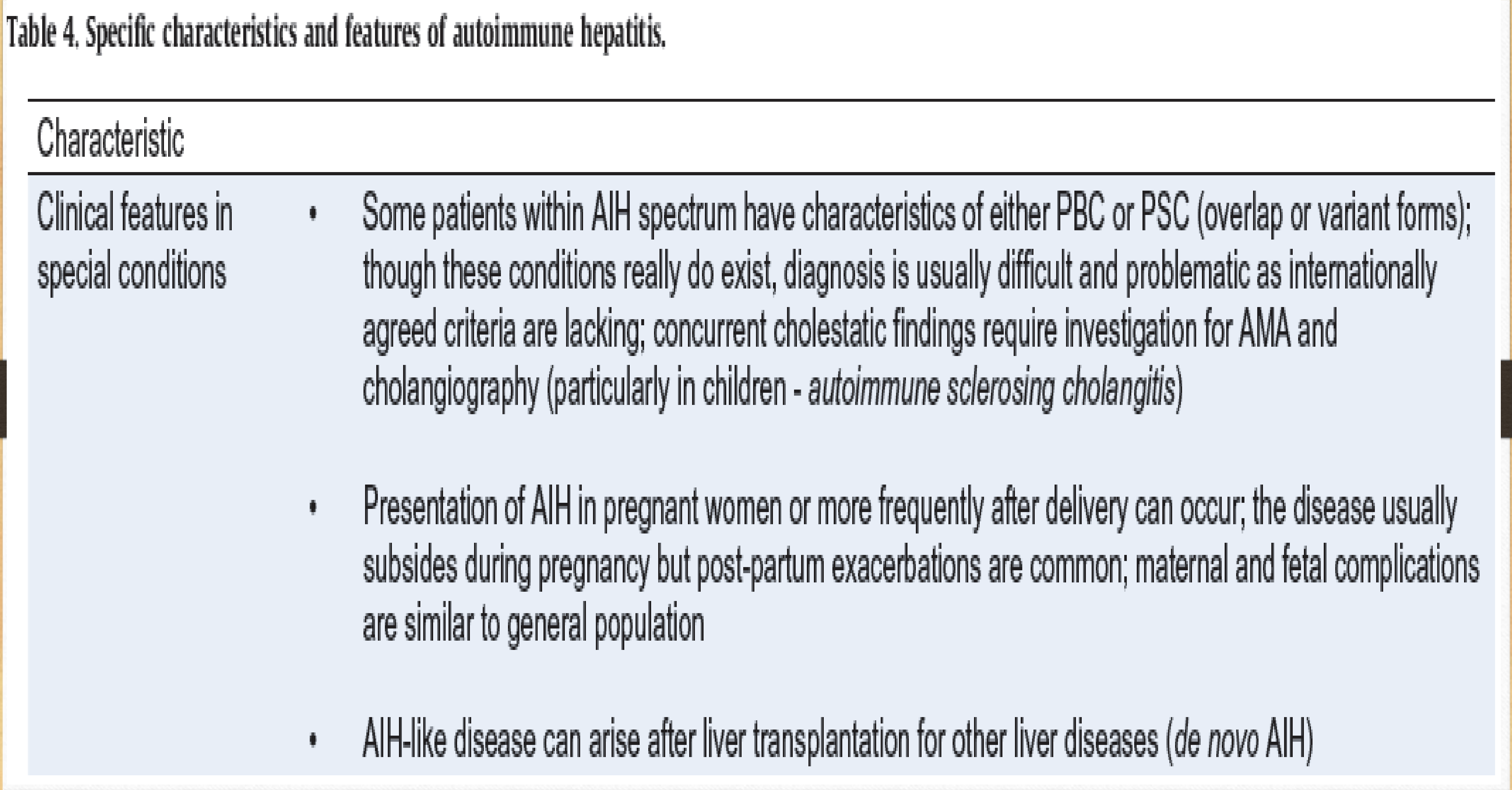
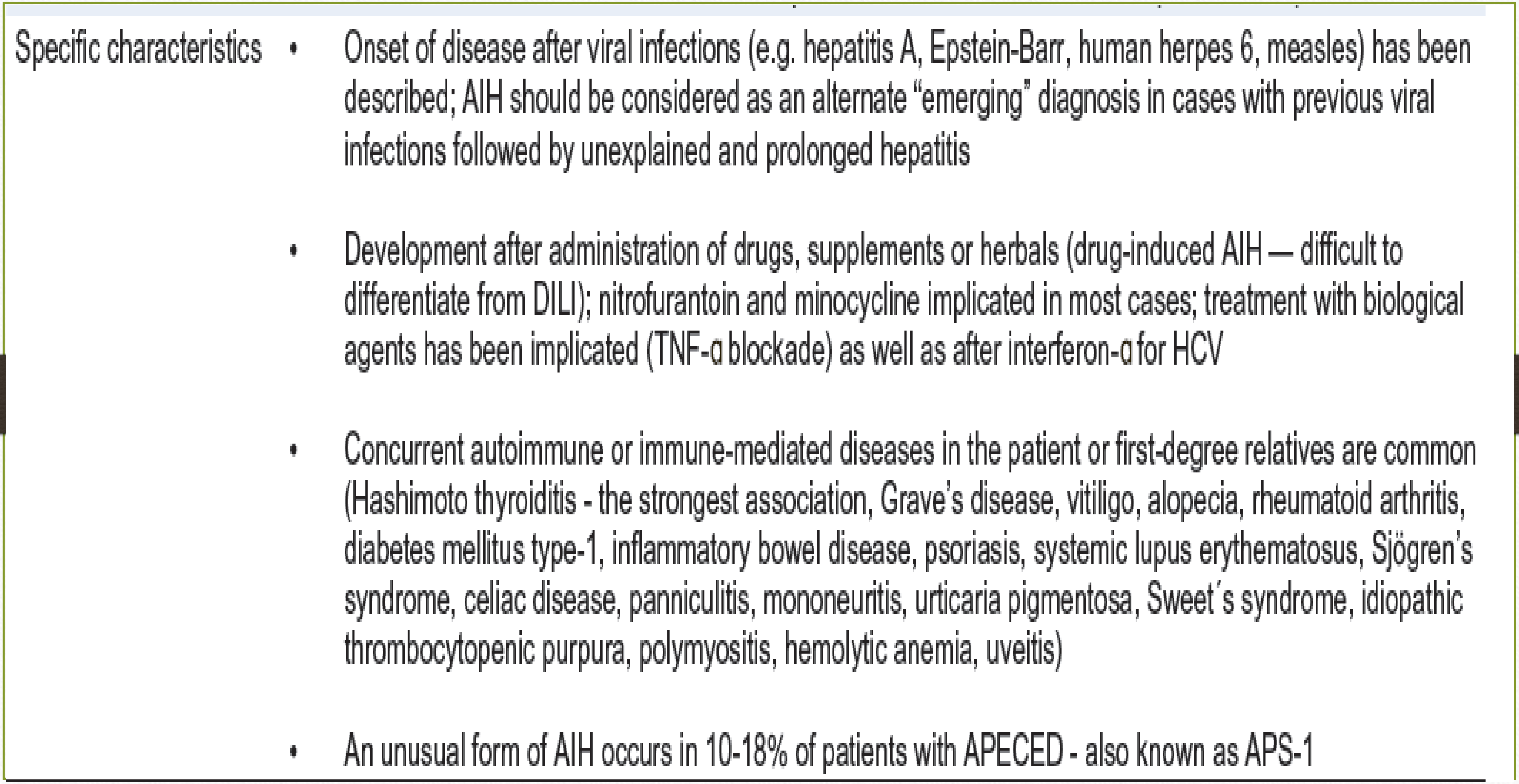


Table 4. Specific characteristics and features of autoimmune hepatitis.

Characteristic	
Clinical features in special conditions	• Some patients within AIH spectrum have characteristics of either PBC or PSC (overlap or variant forms); though these conditions really do exist, diagnosis is usually difficult and problematic as internationally agreed criteria are lacking; concurrent cholestatic findings require investigation for AMA and cholangiography (particularly in children - *autoimmune sclerosing cholangitis*) • Presentation of AIH in pregnant women or more frequently after delivery can occur; the disease usually subsides during pregnancy but post-partum exacerbations are common; maternal and fetal complications are similar to general population • AIH-like disease can arise after liver transplantation for other liver diseases (*de novo* AIH)



Specific characteristics	• Onset of disease after viral infections (e.g. hepatitis A, Epstein-Barr, human herpes 6, measles) has been described; AIH should be considered as an alternate "emerging" diagnosis in cases with previous viral infections followed by unexplained and prolonged hepatitis • Development after administration of drugs, supplements or herbals (drug-induced AIH — difficult to differentiate from DILI); nitrofurantoin and minocycline implicated in most cases; treatment with biological agents has been implicated (TNF-α blockade) as well as after interferon-α for HCV • Concurrent autoimmune or immune-mediated diseases in the patient or first-degree relatives are common (Hashimoto thyroiditis - the strongest association, Grave's disease, vitiligo, alopecia, rheumatoid arthritis, diabetes mellitus type-1, inflammatory bowel disease, psoriasis, systemic lupus erythematosus, Sjögren's syndrome, celiac disease, panniculitis, mononeuritis, urticaria pigmentosa, Sweet´s syndrome, idiopathic thrombocytopenic purpura, polymyositis, hemolytic anemia, uveitis) • An unusual form of AIH occurs in 10-18% of patients with APECED - also known as APS-1

2. **AIH should be considered in any patient with acute or chronic liver disease, particularly in the context of hypergammaglobulinemia (II-2)**

3. **Prompt and timely diagnosis is crucial as untreated AIH has a high mortality rate (I)**

4. Approximately 1/3 of adult patients and about 1/2 of children with AIH have cirrhosis at presentation **(II-2)**
5. Acute presentation of AIH can occur and may manifest as acute exacerbation form of previously undiagnosed AIH or new onset acute AIH without histological changes

6. AIH is associated with a broad variety of other autoimmune diseases **(II-2)**

7. All children with a diagnosis of AIH should undergo
(MR-) cholangiography to exclude autoimmune sclerosing cholangitis

8. AIH patients with cirrhosis should undergo liver ultrasound in six-month-intervals for HCC screening **(II-2)**

9. Counselling for UV-protective measures should be considered for patients on immunosuppressants. Dermatological monitoring for non-melanoma skin cancer after long-term immunosuppressant treatment may be considered **(III)**

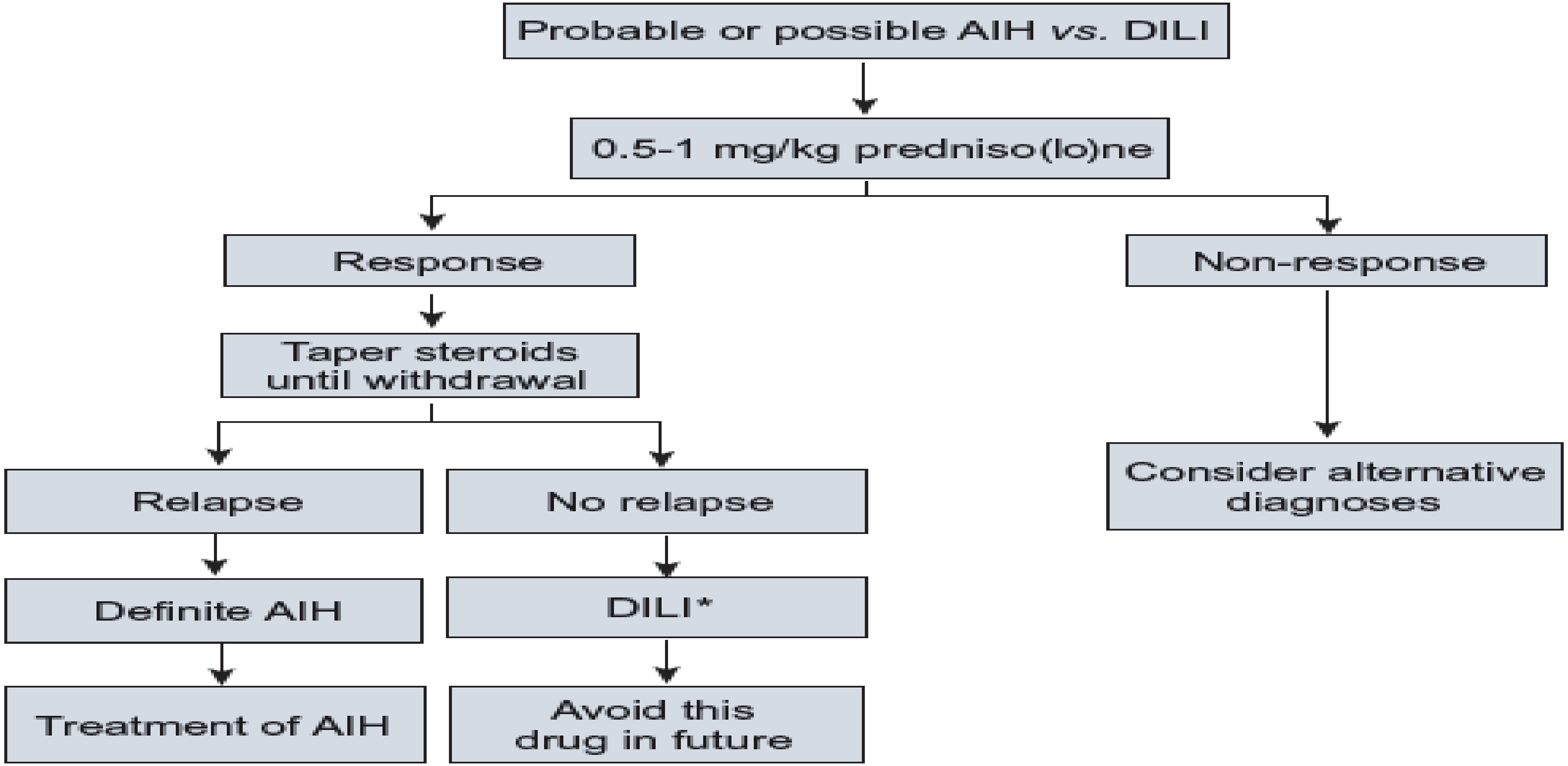


Fig. 1. Suggested diagnostic algorithm for autoimmune hepatitis using routine autoantibody testing by indirect immunofluorescence (IFL) and enzyme linked immunosorbent assay (ELISA) testing with a set of four autoantibodies. A liver biopsy is always required for the demonstration of inflammatory hepatitis, as well as for staging and grading of the liver disease. *Long-term follow-up is advised in order not to miss a late relapse of AIH (e.g. 6 monthly for 3 years).

DILI and AIH

The relationship between DILI and AIH is complex and not fully understood. In principle, three scenarios are possible [69,70]:

1. DILI with a strong immunoallergic component mimicking AIH
2. AIH mimicking as DILI due to drug exposure in recent weeks and spontaneous improvement after cessation of drug exposure
3. AIH triggered by an offending drug (DILI-induced AIH)

Drug-induced AIH has been particularly well described for drugs no longer in use such as tienilic acid and dihydralazine [71,72]. Reactive metabolites created through hepatic metabolism of drugs have been shown to bind to cellular proteins such as components of CYP450, i.e. CYP2C9 in the case of tienilic acid and CYP1A2 in the case of dihydralazine. These can then be recognized by the immune system as neoantigens [71,72]. Among drugs still widely used, drug-induced AIH has been well documented for nitrofurantoin and minocycline

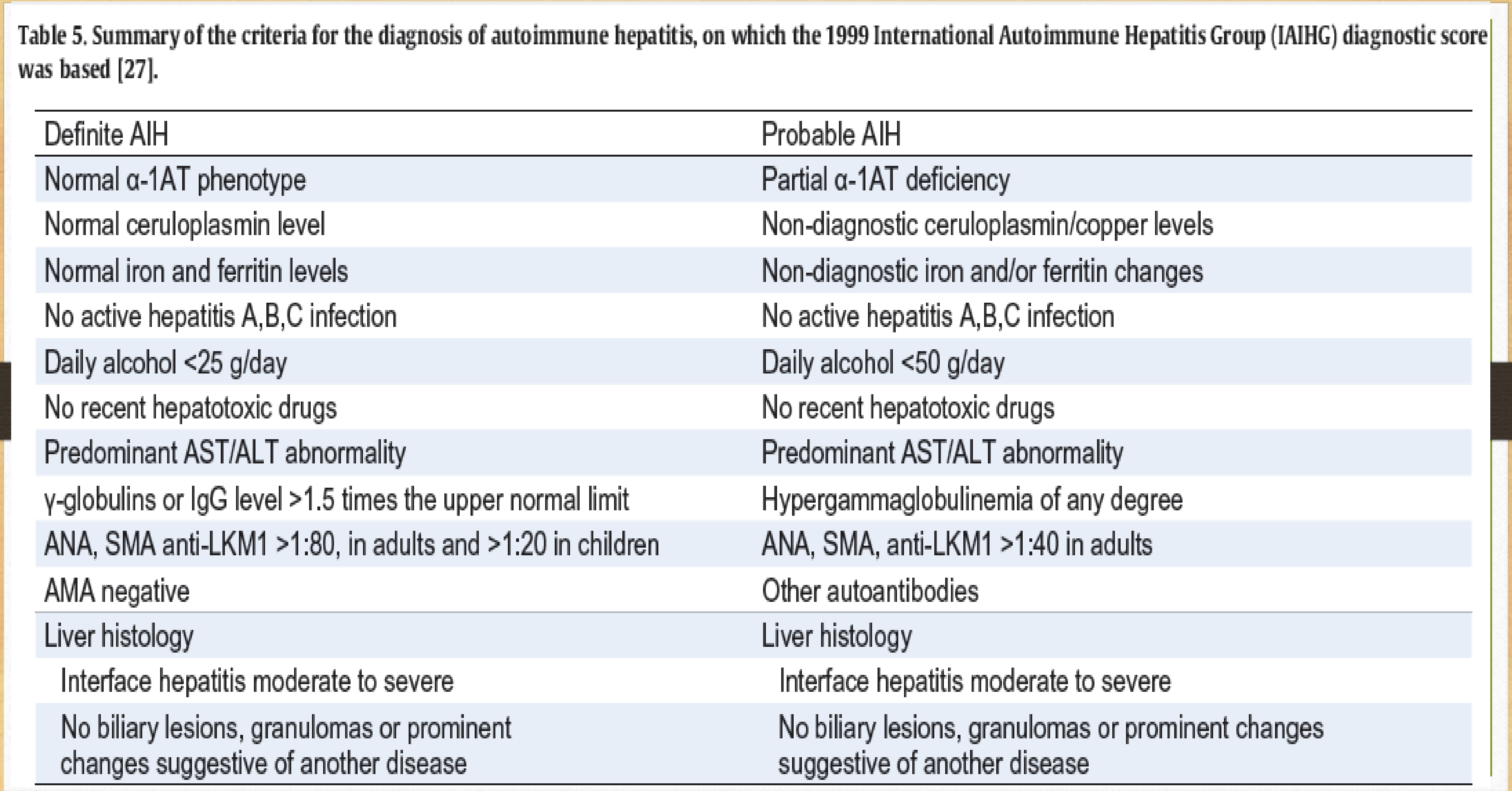


Table 5. Summary of the criteria for the diagnosis of autoimmune hepatitis, on which the 1999 International Autoimmune Hepatitis Group (IAIHG) diagnostic score was based [27].

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
Daily alcohol <25 g/day	Daily alcohol <50 g/day
No recent hepatotoxic drugs	No recent hepatotoxic drugs
Predominant AST/ALT abnormality	Predominant AST/ALT abnormality
γ-globulins or IgG level >1.5 times the upper normal limit	Hypergammaglobulinemia of any degree
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	Liver histology
Interface hepatitis moderate to severe	Interface hepatitis moderate to severe
No biliary lesions, granulomas or prominent changes suggestive of another disease	No biliary lesions, granulomas or prominent changes suggestive of another disease

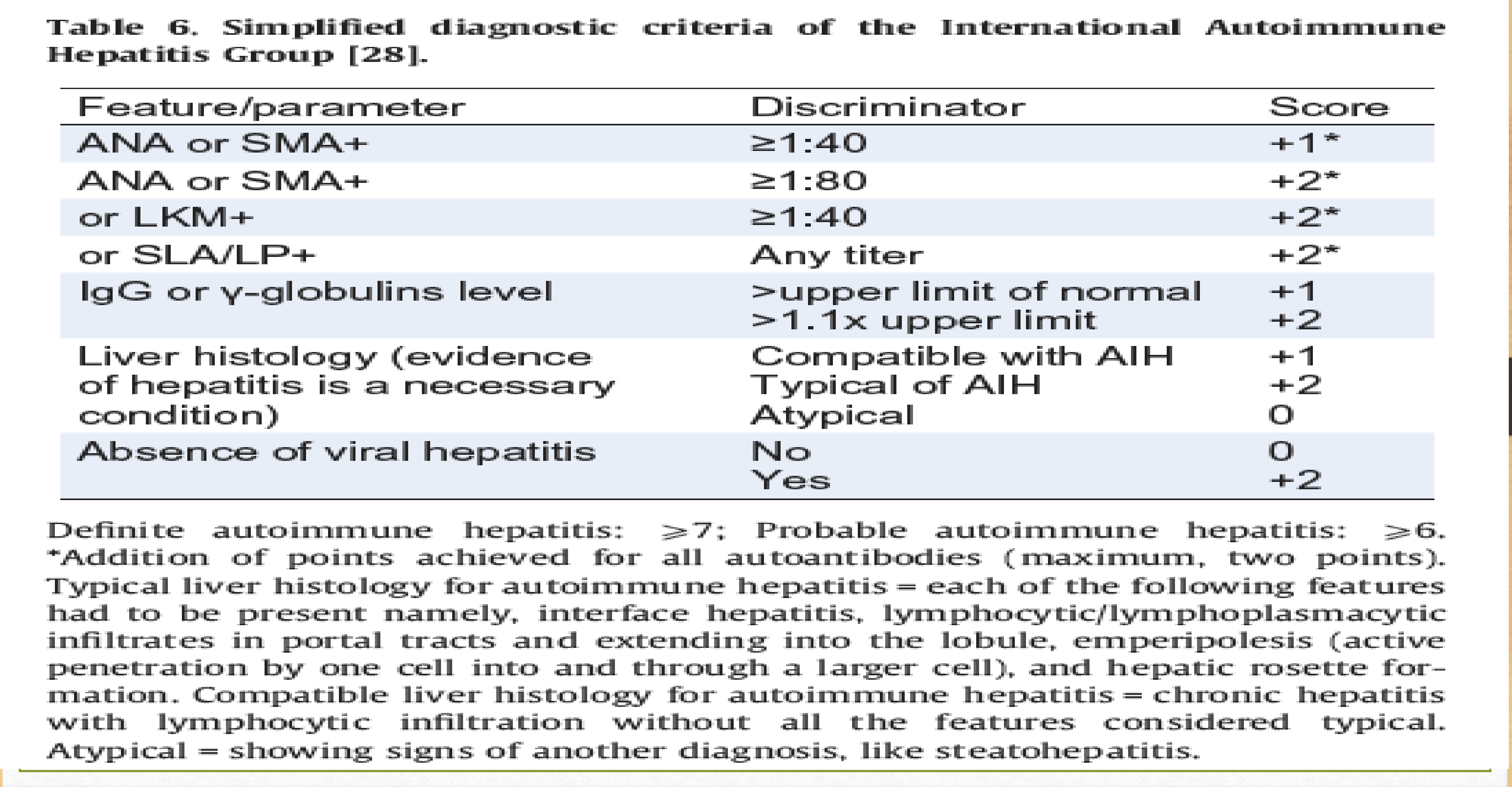
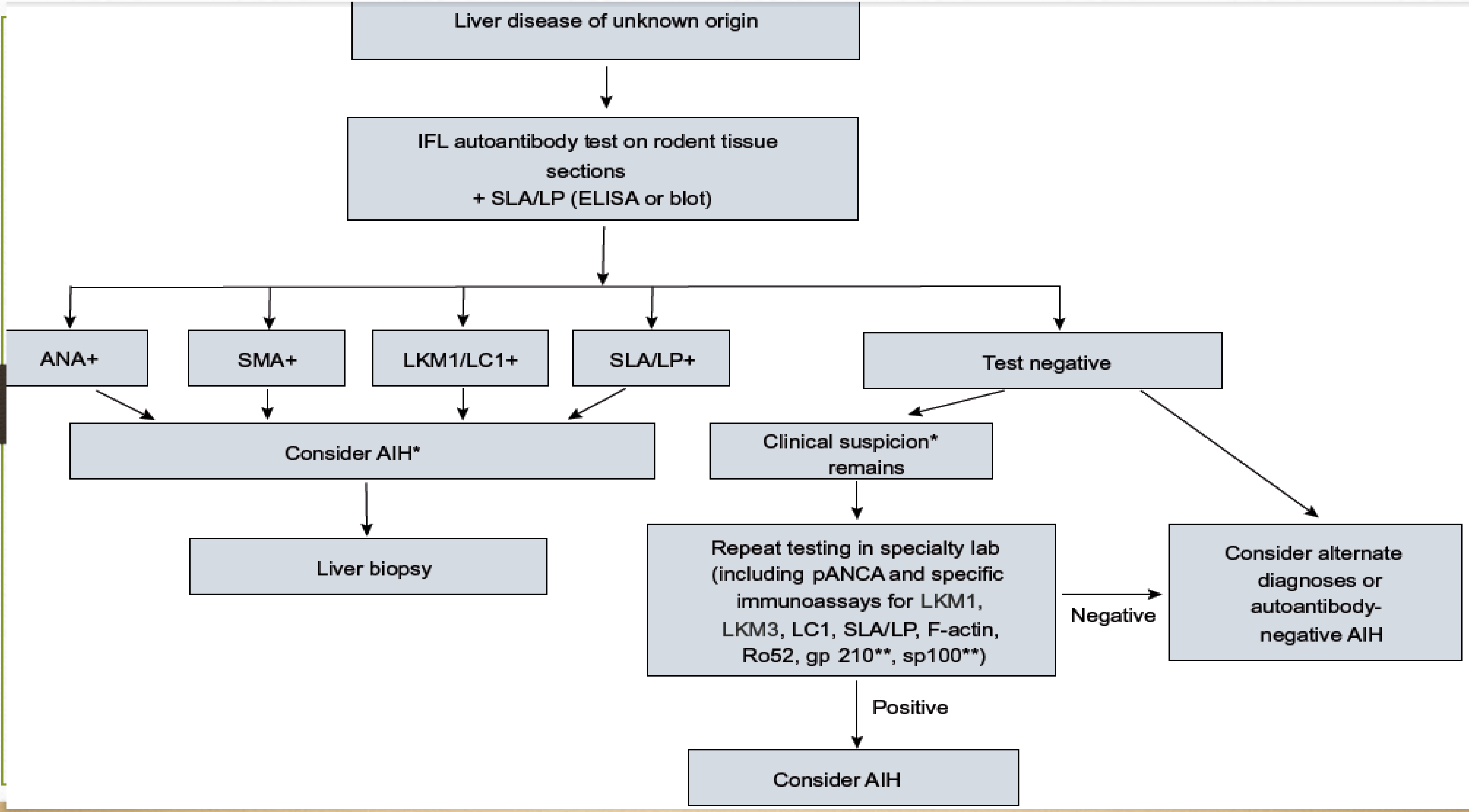


Table 6. Simplified diagnostic criteria of the International Autoimmune Hepatitis Group [28].

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

Definite autoimmune hepatitis: ⩾7; Probable autoimmune hepatitis: ⩾6. *Addition of points achieved for all autoantibodies (maximum, two points). Typical liver histology for autoimmune hepatitis = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation. Compatible liver histology for autoimmune hepatitis = chronic hepatitis with lymphocytic infiltration without all the features considered typical. Atypical = showing signs of another diagnosis, like steatohepatitis.



Liver disease of unknown origin

IFL autoantibody test on rodent tissue sections
+ SLA/LP (ELISA or blot)

ANA+

SMA+

LKM1/LC1+

SLA/LP+

Test negative

Consider AIH*

Clinical suspicion* remains

Liver biopsy

Repeat testing in specialty lab (including pANCA and specific immunoassays for LKM1, LKM3, LC1, SLA/LP, F-actin, Ro52, gp 210**, sp100**)

Negative

Consider alternate diagnoses or autoantibody-negative AIH

Positive

Consider AIH

10. AIH is a clinical diagnosis. The diagnosis of AIH relies particularly on the presence of autoantibodies, hypergammaglobulinemia and typical or compatible histology **(II-2)**

11. The presence of elevated IgG levels, especially in the absence of cirrhosis, is a distinctive feature of AIH. A selectively elevated IgG in the absence of IgA and IgM elevation is particularly suggestive of AIH **(II-3)**

12. Normal IgG or γ-globulin levels do not preclude the diagnosis of AIH. Most of these patients demonstrate a fall of IgG levels upon treatment **(III**

13. Circulating non-organ specific antibodies are present in the vast majority of AIH patients. Autoantibody profiles have been used for sub-classification of AIH.

- AIH-1 (ANA and/or SMA positive)
- AIH-2 (LKM1, LKM3 and/or LC-1 positive)
- AIH-3 (SLA/LP positive).

The clinical implications arising from this subclassification are uncertain **(II-2)**

14. Indirect immunofluorescence is the test of choice for the detection of ANA, SMA, LKM and LC-1. Immunoassays (ELISA/Western blotting) are the tests of choice for the detection of SLA/LP. Methods and cutoff values should be reported by the laboratory **(III)**

15. **Histological demonstration of hepatitis is a prerequisite for the diagnosis of AIH and needs to be part of the initial diagnostic work-up** (II-2)

16. There are no morphological features that are pathognomonic of AIH, but interface hepatitis, periportal necrosis, emperipolesis and rosetting of hepatocytes are suggestive of AIH. These features should be reported by the pathologist in addition to grading (hepatitis activity index) and staging of disease

(II-2)

17. Pericentral necrosis may be present in the acute onset of AIH and histologically indistinguishable from DILI **(II-3)**

18. The simplified scoring system (2008) of the IAIHG
is a useful tool for every day clinical practice **(II-2)**
By considering response to treatment, the revised scoring system (1999) of the IAIHG can be helpful in diagnosing difficult cases **(II-2)**

19. Adult patients with AIH and cholestatic lab changes should be considered for (MR) cholangiography to recognize sclerosing cholangtitis

20. Co-existence of features of AIH and cholestatic liver diseases can be observed, both at diagnosis and during follow-up.Diagnostic tests for PBC and PSC should be performed in patients showing features of cholestasis **(II-2)**

Variant forms of AIH and cholestatic liver disease

Some patients within the spectrum of AIH present either simultaneously
or consecutively, with clinical, biochemical, serological,
and/or histological characteristics of PBC or PSC [51]. Vice versa, some patients with a diagnosis of PBC or PSC show or develop features of AIH. So far, several terms have been used to describe these phenomena, in particular “overlap syndromes”, but also “the hepatitic forms of PBC ”, “secondary autoimmune hepatitis“**autoimmune cholangitis'', ''autoimmune sclerosing cholangitis'' or**
''combined hepatitic/cholestatic syndromes'' to describe patients with features of both AIH and PBC or PSC

The “Paris criteria” are currently the most commonly used tool for diagnosing AIH-PBC variant form as attested by the presence of at least two of the three accepted key criteria of each disease namely, for PBC: 1) alkaline phosphatase (ALP) P2 upper normal limit (ULN) or c-glutamyl-transpeptidase (c-GT) P5 ULN; 2) presence of antimitochondrial antibodies (AMA); 3) a liver biopsy specimen showing florid bile duct lesions; and for AIH: 1) alanine aminotransferase (ALT) P5 ULN; 2) serum IgG levels P2 ULN or presence of SMA, 3) a liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

Features of both AIH and PSC. The co-existence of features of AIH and features of PSC variant has been described both in children and adults and is assumed to exist in a considerable part of mainly young patients with autoimmune liver disease [51–54,61]. Unfortunately, diagnostic criteria for these conditions are even less well-defined than in AIH-PBC variant cases. As a result, reported prevalence figures vary greatly but an approximate prevalence of 7–14% is generally assumed [51]. The diagnosis of large duct PSC should always be established on typical cholangiographic findings, keeping in mind that an intrahepatic biliary tree which simulates a sclerosing pattern can also be observed in any liver disease with extensive fibrosis and nodular regeneration or in cirrhosis

In addition, magnetic resonance cholangiopancreatography (MRCP) may lead to false positive diagnosis due to its limited specificity. Some cases of small duct PSC (normal cholangiogram)-AIH variant forms have also been reported, but it can be argued that approximately 10% of patients with typical AIH, with or without ulcerative colitis, may have histological features of bile duct injury, thus making this diagnosis particularly uncertain [63]. In clinical practice, the diagnosis of AIH-PSC “variants” is made in a patient with overt cholangiographic or histological features of PSC, alongside robust biochemical, serological and histological features of AIH.

IgG4-related AIH. In the emerging era of IgG4-related diseases, the
role of IgG4 response has been investigated in AIH patients [66,67]. Typically IgG4 disease in the liver manifests as a differential
diagnosis of PSC with features of cholangiopathy and jaundice. Despite anecdotal reports from Japan, confirmation is
lacking. Therefore it is difficult to judge, if an entity of AIH-like IgG4 disease exists and presents a separate disease entity

In summary, based on the current, very limited knowledge about the aetiopathogenesis of AIH, PBC, and PSC, definition of diagnostic criteria for these “variant forms” of AIH are very difficult to be established and can only be arbitrary. Consequently, patients with autoimmune liver diseases should rather be categorized according to the primary clinical and histological manifestation of the disease as AIH, PBC, or PSC, and additional features of the respective other immune-mediated liver disease should be listed as such (e.g. PBC with features of AIH).

In addition,
the low prevalence of these variants has made it impractical
to perform randomised controlled trials for their management.
However, as these variant conditions do occur quite frequently,
specific therapeutic considerations may be required in patients
with PBC or PSC with features of AIH [68]. In general, features
of AIH should be managed like AIH, as untreated AIH has a poor
prognosis, but response to therapy is generally very good.

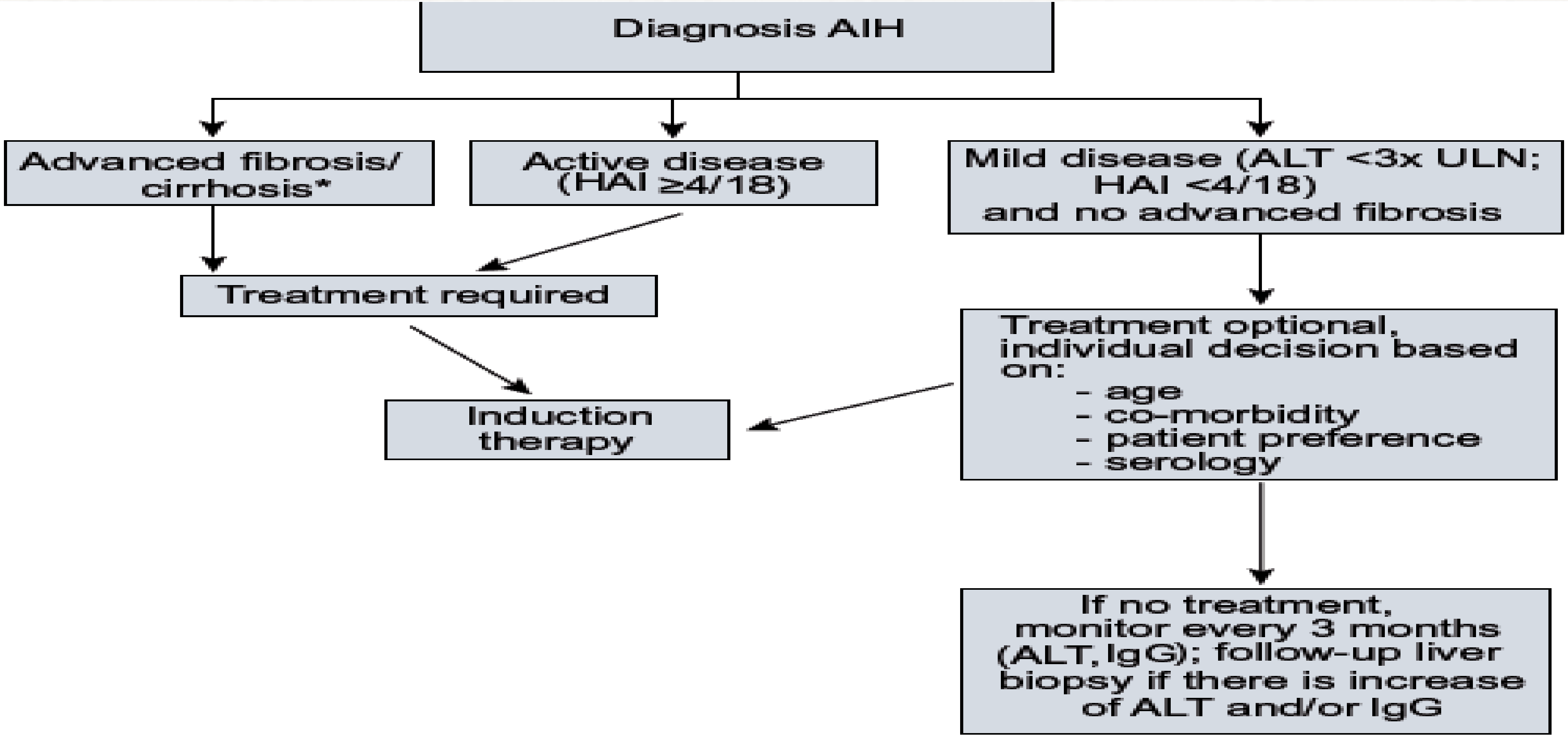
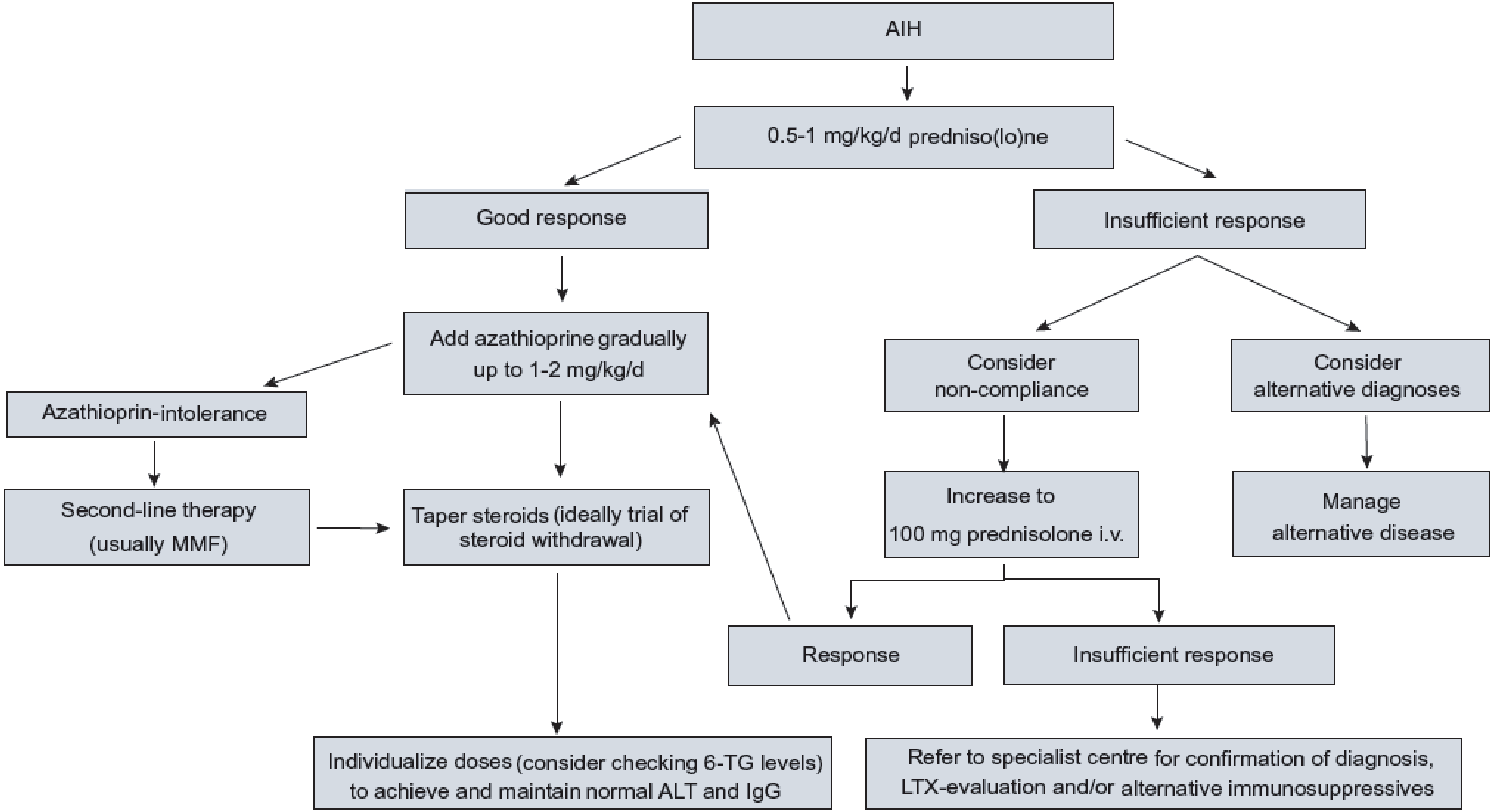


Fig. 3. Therapeutic algorithm with case-by-case decisions about commencing steroid therapy, informed by baseline assessments. For example, a patient with active disease (elevated transaminases >3 normal values and hepatitis activity index (HAI) >4/18) requires treatment. *Treatment probably no longer indicated in decompensated, burn-out cirrhosis, unless high inflammatory score on liver biopsy.

21. **Treatment of AIH should be aimed to obtain complete biochemical and histological resolution of the disease in order to prevent further progression of liver disease (II-2)**

22. **The management of patients with AIH should also include early recognition of extra-hepatic manifestations and symptoms, and associated autoimmune diseases as well as surveillance for disease specific, and treatment-associated complications (III)**

23. All patients with active AIH should be treated (I)
Dosage of therapy should be adapted to the activity of the disease (III)
Only patients in (spontaneous) remission may not require therapy but must be closely followed (three-six monthly) (III)


AIH

0.5-1 mg/kg/d predniso(lo)ne

Good response

Insufficient response

Add azathioprine gradually up to 1-2 mg/kg/d

Azathioprin-intolerance

Second-line therapy (usually MMF)

Taper steroids (ideally trial of steroid withdrawal)

Consider non-compliance

Consider alternative diagnoses

Increase to 100 mg prednisolone i.v.

Manage alternative disease

Response

Insufficient response

Individualize doses (consider checking 6-TG levels) to achieve and maintain normal ALT and IgG

Refer to specialist centre for confirmation of diagnosis, LTX-evaluation and/or alternative immunosuppressives

Fig. 4. Therapeutic strategy in autoimmune hepatitis. Treatment requires induction of remission and prolonged maintenance therapy. Induction is delivered by steroids and thiopurines are added as steroid sparing strategy. Laboratory endpoints are normalisation of IgG and ALT. MMF, mycophenolate mofetil.

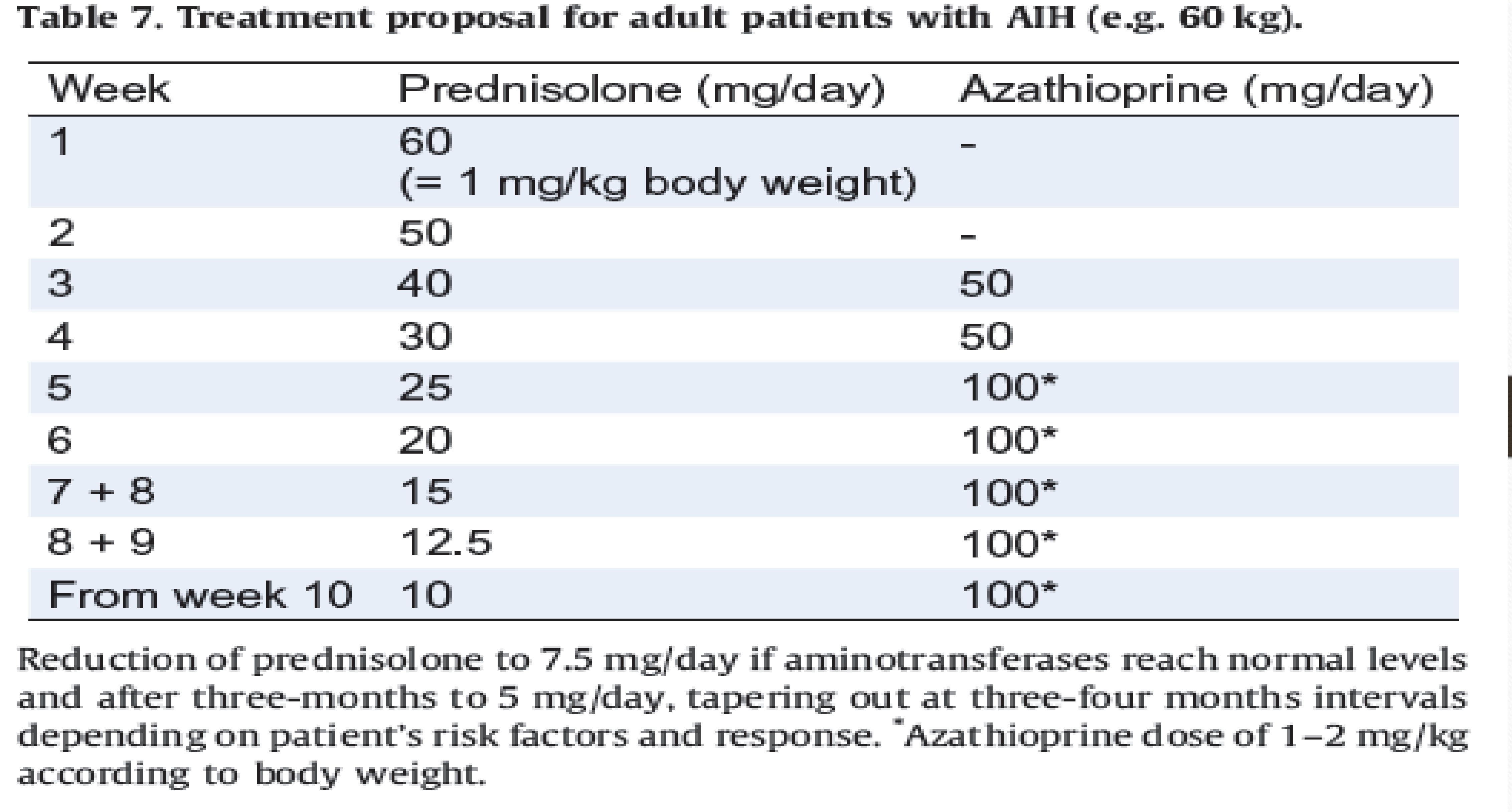


Table 7. Treatment proposal for adult patients with AIH (e.g. 60 kg).

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*

Reduction of prednisolone to 7.5 mg/day if aminotransferases reach normal levels and after three-months to 5 mg/day, tapering out at three-four months intervals depending on patient's risk factors and response. *Azathioprine dose of 1–2 mg/kg according to body weight.

24. **Predniso(lo)ne as initial therapy followed by the addition of azathioprine after two weeks is the first line treatment of AIH (I)**
Initial dose of predniso(lo)ne should be between 0.5 and 1 mg/kg/day. Higher initial doses can induce remission more quickly albeit at the expense of steroid related side effects (II-2)

25. Azathioprine can be initiated whenever bilirubin levels are below 6 mg/dl (100 µmol/L) and ideally two weeks after the initiation of steroid treatment. The initial dosage should be 50 mg/day, and increased depending on toxicity and response up until a maintenance dose of 1-2 mg/kg **(II-2)**

26. Treatment of AIH should be response guided and treatment regimens should be individualised **(III)**

27. A failure of adequate response should lead to a reconsideration of diagnosis or re-evaluation of adherence to treatment **(II-2)**

28. In patients with sub-optimal response despite reconfirmation of diagnosis and adherence, dosage of prednisolone and azathioprine should be increased or alternative medications should be used (please see section on “difficult to treat patients”) **(II-2)**

29. Patients with acute severe AIH should be treated with high doses of intravenous corticosteroids (≥1 mg/kg) as early as possible. Lack of improvement within seven days should lead to listing for emergency liver transplantation **(III)**

30. Biochemical remission is defined as normalisation of IgG and transaminases. Histological remission is defined as normal histology or minimal hepatitis (HAI <4 or equivalent) **(II-2)**

31. Immunosuppressive treatment should be continued for at least three years and for at least two years following complete normalisation of transaminases and IgG **(II-2)**

32. In patients without biochemical remission, treatment should not be discontinued. In patients who have been in biochemical remission for more than two years, a liver biopsy should be considered prior to treatment withdrawal. In patients with continued histological disease activity (HAI >3), treatment should also not be discontinued (II-2)

33. Only a small minority of patients stay in remission without maintenance therapy. A trial of treatment withdrawal requires close cooperation between patient and physician. A relapse occurs most commonly within 12 months after treatment withdrawal. However, relapse may even occur many years later. Patients should therefore be closely monitored after treatment withdrawal, and surveillance continued lifelong. An increase in IgG can precede the rise of transaminases in a relapse (II-2)

34. Treatment of the relapse or flare may require steroid doses similar to the induction regimen. Earlier detection of relapse allows lower doses of immunosuppressants to re-induce full remission (II-2)

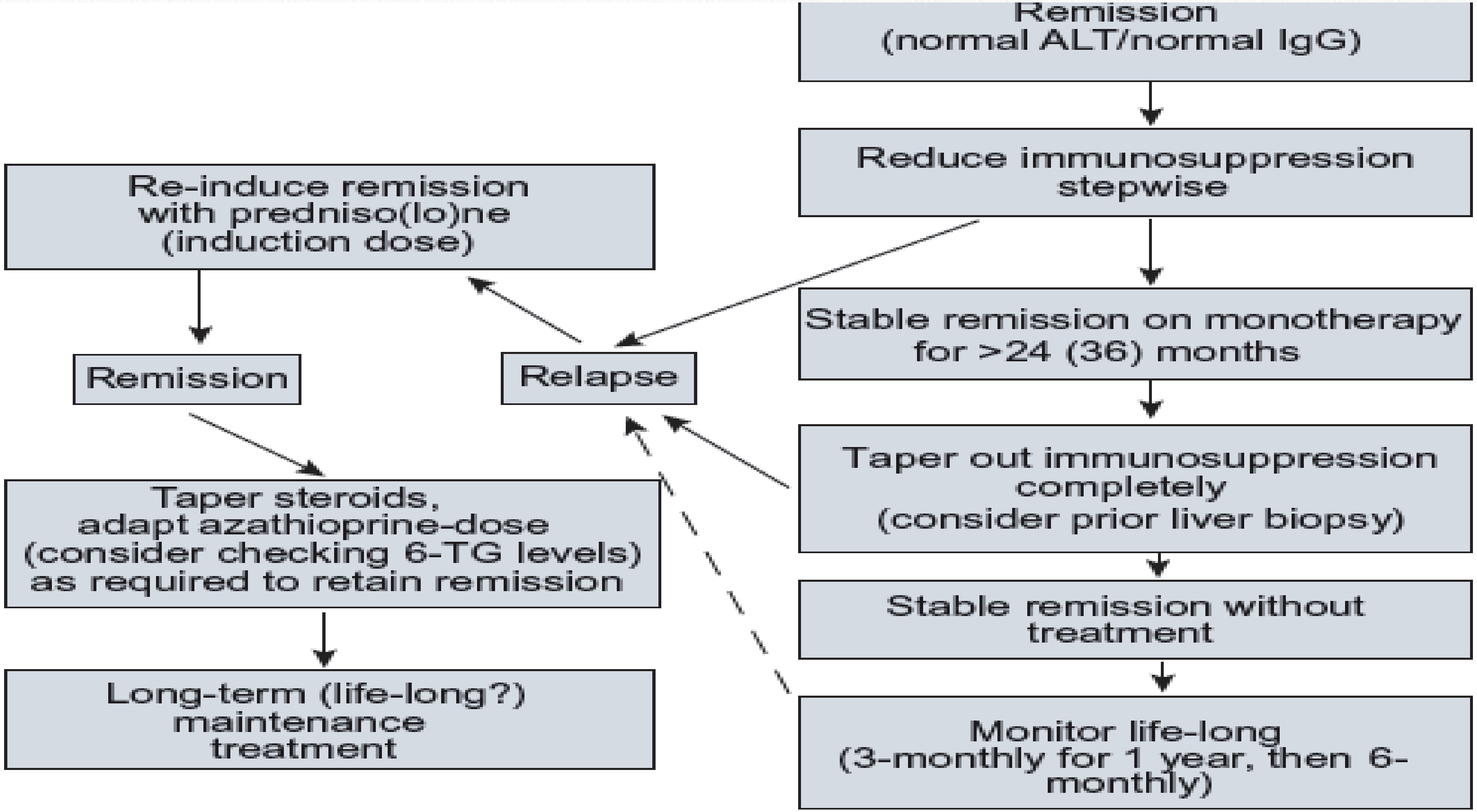
35. Patients who have received adequate immunosuppression and have relapsed during drug withdrawal, or who experienced a flare during adequate maintenance therapy should be kept on immunosuppression permanently **(II-2)**

36. In patients with mild disease and intolerant to azathioprine, prednisolone monotherapy can be considered **(II-2)**

37. In all other patients, steroid-free monotherapy with azathioprine (or MMF) should be the goal of maintenance therapy. Maintenance treatment should be adapted in dose to sustain stable remission with normalised transaminases and IgG levels. The rate of relapse after prednisolone withdrawal can be reduced by application of azathioprine at a dose of up to 2 mg/kg/day **(II-2)**

38. **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)**

39. Controlled AIH is neither a contraindication to pregnancy nor to breastfeeding **(II-2)**
Maintenance treatment of azathioprine plus/minus predniso(lo)ne should be continued **(II-2)**
Mild flares can occur in the first trimester and in particular after delivery and may require transient increase in immunosuppression **(II-2)**
MMF is contraindicated in pregnancy **(II-2)**



Remission
(normal ALT/normal IgG)

Reduce immunosuppression stepwise

Stable remission on monotherapy for >24 (36) months

Taper out immunosuppression completely
(consider prior liver biopsy)

Stable remission without treatment

Monitor life-long
(3-monthly for 1 year, then 6-monthly)

Relapse

Re-induce remission with predniso(lo)ne
(induction dose)

Remission

Taper steroids, adapt azathioprine-dose (consider checking 6-TG levels) as required to retain remission

Long-term (life-long?) maintenance treatment

Fig. 5. Follow-up of autoimmune hepatitis patients who have achieved remission. Note that drug-free remission of autoimmune hepatitis is infrequent and cannot be achieved in the majority of patients.

40. Children with AIH require higher doses of steroid at initiation of therapy. The principles of management of AIH in children are otherwise similar as in adults **(II-2)**

41. **Measurement of bone density is recommended at the initiation of steroid therapy. Supplementation of Vitamin D and adequate calcium intake should be recommended to all patients receiving steroid therapy**

42. In patients requiring high dose, long-term (>20 mg/day) steroid therapy, conventional treatment should be optimized (high doses of predniso(lo)ne combined with 2 mg/kg/day azathioprine). Alternatively, a trial of CNIs (ciclosporine or tacrolimus), infliximab, methotrexate, or cyclophosphamide can be initiated. The relative effectiveness of second line treatments has not been examined in clinical trials. Therefore, these drugs should be used after consultation with a specialist centre only (II-3)

43. In patients with incomplete response under budesonide-based regimen, replacement of budesonide with predniso(lo)ne (>20 mg/day initially) should be considered **(III)**

44. In patients with incomplete response under azathioprine-predniso(lo)ne-based regimen, increasing the dose of azathioprine to 2 mg/kg/day, together with 5-10 mg/day predniso(lo)ne may be tried, with repeat liver biopsy after a further 12-18 months **(II-3)**

45. Complete response may not be attainable in some patients and the goal should be the lowest achievable biochemical activity with a minimum of side effects. Histological control of treatment effect and/or disease progression may be necessary **(II-3)**

46. Maintaining treatment-adherence is of particular importance in adolescents and young adults **(II-2)** Management of the transition to adult care is better achieved in specialised transition services with a multidisciplinary approach **(II-3)**

47. In patients without cirrhosis, budesonide plus azathioprine may be used as induction therapy and can be considered for patients with co-morbidities that might be exacerbated by predniso(lo)ne treatment **(II-2)** Long-term data on budesonide safety and efficacy in AIH are lacking **(I)**

48. If adequately dosed therapy with azathioprine is insufficient to maintain remission in predniso(lo)ne responders with severe steroid side effects, a switch from predniso(lo)ne to budesonide may be considered **(II-3)**

49. In patients intolerant to azathioprine, mycophenolate is the second line drug of choice **(II-2)**

The relative efficacy and tolerability of MMF in other patients compared to azathioprine has not been established **(II-2)**

A trial of 6-MP or 6-TG in patients intolerant to azathioprine is an alternative option **(III)**

50. 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)**

51. **Treatment of AIH following liver transplantation (recurrent or de novo) should follow the standard management principles of AIH (II-3)**

52. Hepatitis A and B vaccination as well as yearly influenza vaccination should be given to all AIH patients **(III)**

53. The heterogeneity and complexity of AIH, requires specialised diagnostic and therapeutic services. Patients should be provided with access to specialised care in order to improve outcome, survival and quality of life; either in specialised centres or through managed clinical networks **(II-3)**

54. There is increased recognition of decreased quality of life in AIH patients. Management of AIH should therefore also address psychosocial needs **(II-2)**