

**UPDATE OF THE BRAZILIAN SOCIETY OF HEPATOLOGY
RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF
AUTOIMMUNE DISEASES OF THE LIVER**

ABSTRACT:

New data concerning the management of autoimmune liver diseases have emerged since the last single-topic meeting sponsored by the Brazilian Society of Hepatology to draw recommendations about the diagnosis and treatment of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), overlap syndromes of AIH, PBC and PSC and specific complications and topics concerning AIH and cholestatic liver diseases. This manuscript updates those previous recommendations according to the best evidence available in the literature up to now. The same panel of experts that took part in the first consensus document reviewed all recommendations, which were subsequently scrutinized by all members of the Brazilian Society of Hepatology using a web-based approach. The updated recommendations are presented in the present manuscript.

HEADINGS: Autoimmune hepatitis. Primary sclerosing cholangitis. Primary biliary cholangitis. Diagnosis. Treatment.

INTRODUCTION

The Brazilian Society of Hepatology published evidence-based recommendations for the management of autoimmune liver diseases (ALD) in December 2015 issue of Archives of Gastroenterology, following a consensus meeting held in São Paulo on October 18th, 2014 (1). The first version covered diagnosis and treatment of autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and their overlap syndromes; the management of specific complications of cholestasis, such as pruritus, fatigue and hypercholesterolemia and special controversial topics including management of recurrent cholangitis, prevention and management of biliary tract tumors in PSC and liver transplantation (LT) for AIH, PSC and PBC. Since then, a bulk of data concerning the diagnosis and treatment of ALD have emerged in the medical literature and even primary biliary cirrhosis have been properly renamed as primary biliary cholangitis (2). Due to these reasons, the Brazilian Society of Hepatology sponsored another meeting in December 2018 to update the aforementioned recommendations. An organizing committee of five experts, the same who took part in the 1st consensus meeting submitted to the previous panel all topics to be reviewed according to the best-evidence available in literature using MEDLINE. All updated recommendations were discussed by the organizing committee and were further scrutinized by all members of the Brazilian Society of Hepatology using a web-based approach. Most of those updated recommendations were based on new data published since 2015 (3-44), which are briefly summarized in figures 1 to 4. The present manuscripts is the final version of the document followed by the recommendations, which were graded according to the

grading system adopted by the American College of Cardiology and the American Heart Association, as outlined below (3):

- Class I: conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective.

-Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.

-Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.

-Class IIb: usefulness/efficacy is less well established by evidence/opinion.

-Class III: conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful.

UPDATE OF RECOMMENDATIONS

I. AUTOIMMUNE HEPATITIS

Ia. AIH: Clinical manifestations

1. AIH primarily affects women in a 4:1 ratio, mostly in 5 to 25 years of age, but it can occur in all age and races. In the majority of cases, patients with AIH have unrecognized chronic liver disease with acute hepatitis-like symptoms, but signs and symptoms of advanced chronic liver disease may also be present. Less frequently, the disease can be present without symptoms or with fulminant hepatic failure (FHF). Consequently its diagnosis should be considered in any patients with liver disease at any age (Class IIa).

2. Autoimmune extrahepatic disorders, particularly autoimmune thyroiditis and rheumatoid arthritis, are frequently detected in patients with AIH and should be assessed in all subjects with AIH (Class I).
3. AIH in first-degree relatives of patients with the disease is very infrequent, and family screening is not recommended. (Class I)

Ib. AIH: Diagnosis

1. The diagnosis of AIH should be performed in patients with elevated aminotransferases and gammaglobulin levels, reactivity for anti-smooth muscle (SMA), antinuclear (ANA), anti-liver kidney microsome type 1 (anti-LKM1), anti-liver cytosol type 1 (anti-LC1) and anti-soluble liver antigen (anti-SLA) antibodies and typical histological findings, after the exclusion of other liver diseases, particularly viral hepatitis and Wilson's disease (Class I)
2. SMA, ANA, anti-LKM1 and anti-LC1 should be screened by indirect immunofluorescence (IIF) using rodent tissues, while anti-SLA reactivity should be assessed by ELISA or immunoblotting (Class I).
3. In adults, the recommended cut-off titre for autoantibody positivity should be 1:40, since low titres can also be found in healthy subjects and patients with other liver diseases. In children, the recommended cut-off titre for autoantibody positivity should be 1:20 for ANA and SMA or 1:10 for anti-LKM1 (Class I).
4. Only homogeneous and speckled ANA patterns should be considered as AIH markers. (Class IIa)
5. In the presence of anti-LKM1, screening for anti-LC1 antibodies is unnecessary, but if done it must be assessed by techniques with

specific antigens, such as ELISA, immunoblotting or immunodiffusion.

(Class I)

6. If anti-SLA testing is not possible, anti-SSA/Ro seropositivity can be considered an indirect evidence of anti-SLA/LP reactivity, since more than 70% of patients have concomitant reactivity. (Class IIa)
7. The revised International AIH Group (IAIHG) scoring system and the simplified AIH criteria can be used for the diagnosis of AIH, but the former performs better in the diagnostic evaluation of atypical cases (Class IIa). For pediatric patients with AIH, it is important to perform magnetic resonance cholangiopancreatography (MRCP) to exclude autoimmune sclerosing cholangitis, which is very common in this age group (Class IIa).
8. Liver biopsy, whenever possible, should be considered in patients with AIH for histological diagnosis and prognostic assessment. It may not be entirely necessary in patients with classical full-blown disease; however, it should be performed in all non-classical cases, such as AIH in men, absence of classical serological markers or hypergammaglobulinemia and reactivity to antimitochondrial antibodies (AMA). (Class IIb). Pathology reports should describe or rule out the presence of the typical histological findings of the disease, such as emperipolesis, interface hepatitis, plasma cells and rosettes of hepatocytes
9. It is important to distinguish between acute exacerbation of chronic AIH and genuine acute AIH without chronic histological changes. In the second case, autoantibodies can be absent, as well as classical

characteristics of the disease and liver biopsy may show cirrhosis with frequent zone III centrilobular necrosis (Class IIa)

Ic. AIH: Management and treatment of adulthood and pediatric AIH

1. Initial treatment of AIH in adults should be instituted with dual therapy with azathioprine and prednisone in doses, respectively, of 30 mg/day and 50 mg/day, in the absence of known contraindications for the use of those drugs (Class I). In childhood AIH, dual therapy with prednisone 2 mg/kg/day (up to 60 mg/day) and azathioprine 1-2.5 mg/kg/day is also recommended (Class I).
2. Despite the lack of data to guide drug adjustments during immunosuppressive therapy of AIH, it is suggested to taper the dose of prednisone at monthly intervals and to progressively increase the dose of azathioprine to achieve biochemical remission with as minimal side effects as possible of both drugs (Class I).
3. The range of maintenance dose of prednisone and azathioprine are respectively, 7.5-15 mg/day and 75-150 mg/day, not exceeding doses of azathioprine above 2 mg/kg/day. Maintenance doses of those immunosuppressive drugs in children are usually 2.5-5 mg/day for prednisone and up to 2 mg/kg/day for azathioprine. (Class IIb)
4. It is suggested to begin monotherapy with prednisone in AIH patients with contraindications to azathioprine therapy.

Treatment in adults should begin with prednisone 60 mg/day with subsequent tapering to 40 mg/day and then 30 mg/day every two weeks. The corticosteroid dose should be decreased more gradually afterwards to maintenance levels not higher than 20 mg/day. In children, doses of corticosteroids should be tapered to achieve biochemical remission with minimal side effects. (Class IIb)

5. Despite one RCT demonstrating the benefits of budesonide in the treatment of AIH, the use of this drug as first-line therapy of AIH in adults, as well as in children, cannot be routinely recommended. It could be considered in specific cases, such as corticosteroids intolerance or severe side effects, only in patients with early-stage disease with mild-to-moderate fibrosis. (Class IIb).
6. Clinical, biochemical and histological remission of AIH should be regarded as the primary end-point of treatment (Class I). In order to achieve this primary end-point, treatment should be maintained for at least 36 months. Liver biopsy should be performed at least 24 months after biochemical remission in order to assess histological remission (Class I).
7. Biochemical remission is defined as normalization of aminotransferases and IgG levels. Histological remission is defined as normal histology or minimal hepatitis (periportal activity 0 or 1) or Hepatitis Activity Index < 4 (Class I). The persistence of high titers of SMA and/or antiactin antibodies in

patients with AIH is usually associated with disease activity.
(Class IIa).

8. In patients with clinical, biochemical and histological remission, treatment withdrawal may be tried, after discussion of the benefits and risks with the patient. Close monitoring of aminotransferases and liver function is recommended, especially in the first 12 months after treatment withdrawal.
(Class I)
9. It is recommended to perform liver biopsy to confirm histological remission prior treatment withdrawal. (Class I)
10. Monotherapy with azathioprine in doses up to 2mg/kg/day may be instituted as maintenance therapy indefinitely in those subjects not willing to stop treatment (Class IIa)
11. Chloroquine monotherapy can enhance biochemical remission and may be offered to patients with AIH after withdrawal of prednisone and azathioprine (Class IIb)
12. In AIH patients with intolerance to azathioprine, mycophenolate mofetil can be used instead of azathioprine (Class IIb).
13. In patients with suboptimal responses to conventional dual therapy, the measurement of azathioprine metabolites may be helpful to increase treatment response, avoid drug toxicity and monitor treatment adherence. In the presence of low 6-thioguanine levels and/or high levels of 6-methylmercaptopurine, the addition of allopurinol, in centers with local expertise and resources, may be warranted to shift the metabolism of the

azathioprine to a pathway that favors the production of active and/or less toxic metabolites. (Class IIb)

14. In patients with incomplete response, promising alternative drugs include calcineurin inhibitors (Class IIa). Either cyclosporin or tacrolimus may be used in AIH patients due to the absence of randomized controlled trials (RCT) favoring one of those drugs (Class IIa). In children, mycophenolate could be an option for such cases (Class IIb)
15. AIH patients with cirrhosis should undergo screening for hepatocellular carcinoma with ultrasound and measurement of alphafetoprotein levels every 6 months. (Class IIa)
16. AIH per se is not a contraindication to pregnancy nor to breastfeeding. Immunosuppression during pregnancy can be carried out with prednisone and azathioprine, after appropriate discussion with the patient, due to the low risk of fetal teratogenicity seen with azathioprine. Avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant in breast milk, making this drug an acceptable option for this period (Class IIa). Mycophenolate mofetil is contraindicated during pregnancy due to increased risk of fetal malformations, as well as during breastfeeding. (Class I) Prednisone monotherapy is a safer option during pregnancy and breastfeeding. (Class IIb)
17. Hepatitis A and B and influenza vaccination should be offered to all AIH patients (Class IIb)

II. PRIMARY SCLEROSING CHOLANGITIS

Ila. PSC- Diagnosis

1. Patients with cholestasis of unknown cause, particularly in the absence of AMA should be submitted to MRCP to rule out PSC (Class I).
2. Endoscopic retrograde cholangiography (ERC) can be considered, if MRCP plus liver biopsy is equivocal or contraindicated, in patients with persistent clinical suspicion of PSC. The risks of ERC have to be weighed against the potential benefit with regard to surveillance and treatment recommendations. (Class IIa)
3. Liver biopsy should be considered in those subjects with normal MRCP under suspicion of small-duct PSC. Histology is not required for diagnosis of patients with large-duct PSC by MRCP. However, it may be needed to assess the presence of PSC with features of AIH, in those subjects with disproportionately higher aminotransferases levels more than 5 times the upper limit of normal (Class Ib).
4. Colonoscopy is recommended for patients with PSC at diagnosis and every 3-5 years, irrespective of the presence of symptoms. Multiple biopsies are recommended even if the endoscopic appearance of the colonic mucosa is normal. (Class Ia).
5. Patients with the diagnosis of concurrent IBD should be

submitted to annual colonoscopic screening for colorectal neoplasia. In centers with appropriate expertise and resources, consider chromoendoscopy to improve surveillance (Class Ib).

6. Adults with diagnosis of PSC should have IgG-4 serum levels measured to rule out IgG-4 cholangitis for appropriate management

IIb. PSC: Pharmacological treatment

1. After detailed discussion of risks and benefits of therapy and about the limitations of available data, the use of UDCA in intermediate doses (17-23 mg/kg/day) should be considered for adult patients with PSC. (Class IIb)
2. PSC carriers under treatment with UDCA should be regularly monitored with clinical examination and liver tests, to assess response to therapy and to identify possible disease progression. (Class I)
3. In patients treated with UDCA, normalization or significant reduction of serum levels of ALP suggests better prognosis (Class II). There is no evidence that UDCA should be discontinued in the absence of response, except when the progression of the disease is possibly related to UDCA itself (Class II).
4. There is no sufficient evidence to recommend the use of fibrates or other pharmacological alternatives as specific therapies for PSC (Class IIb).

5. Immunosuppression with corticosteroids alone or in combination with azathioprine is recommended in cases of PSC with AIH-like characteristics and for the treatment of PSC associated IgG4 (Class I).
6. There is no evidence that the use of UDCA reduces the risk of developing colon cancer or gallbladder cancer in patients with PSC (Class III).
7. Pregnancy is generally well tolerated in women with compensated PSC, but there seems to be an increased risk of preterm birth (Class II). The use of UDCA can be considered during pregnancy, preferably after the first quarter (Class II).

IIc. PSC: Endoscopic treatment

1. Endoscopic treatment can be indicated in centers with expertise in therapeutic ERC in subjects with PSC with dominant strictures (Class IIb).
2. Dominant stricture is defined as a stenosis with a diameter <1.5 mm in the common bile duct or <1 mm in a hepatic duct. (Class I)
3. Ductal sampling (brush cytology and/or endobiliary biopsies) during ERCP is recommended for all patients with PSC and dominant strictures to rule out CCC. (Class IIb) Brush cytology coupled with fluorescence in situ hybridization (FISH) can increase the sensitivity of cytologic samples and should be performed if available (Class I).
4. Routine administration of prophylactic antibiotics before ERC in

patients with PSC is warranted (Class IIb).

5. ERC with balloon dilatation is the recommended approach in symptomatic patients with PSC and DS (Class I). Stent placement after dilation is not routinely recommended as it can increase the risk of bacterial cholangitis (Class III). Stenting can be necessary for a short period of time in cases of severe strictures (Class IIa).

IId. PSC: Diagnostic and therapeutic implications in children

1. Due to the scarcity of cases of PSC in children, it is not possible to establish evidence-based recommendations for the management of the disease in the pediatric age group (Class I).
2. Clinical manifestations are similar to those observed in adults. Dominant strictures and CC is rarely seen. On the contrary, AIH and PSC overlap is much more common (Class IIa).
3. MRCP is the procedure of choice for diagnosis of PSC in children. Liver biopsy is usually necessary to rule out other common causes of secondary sclerosing cholangitis (Class IIa).
4. Colonoscopy should be performed to assess concurrent IBD (Class IIa)
5. There is scarcity of data concerning treatment options for PSC in children (Class I).

III. PRIMARY BILIARY CIRRHOSIS:

IIIa. PBC: Diagnosis

1. AASLD criteria should be adopted for initial evaluation of PBC patients (Class I).
2. The diagnosis of PBC is established when 2 of the following criteria are met: sustained elevation of ALP; presence of AMA or other PBC-specific autoantibodies (including sp100 or gp210, if AMA is negative) and liver biopsy demonstrating non-suppurative destructive cholangitis and destruction of interlobular bile ducts.
3. Regarding autoantibodies: AMA titers $\geq 1:80$ are considered significant. Anti-M2 antibodies should be ordered either if AMA is negative or if the titer of AMA is $< 1:80$ or its pattern is not typical (Class I).
4. Testing for ANA and pattern characterization [nuclear dots (sp100) or nuclear envelope (gp210)] by indirect immunofluorescence in HEp-2 cells or by immunoblotting and ELISA must be requested in AMA negative patients, to assess for PBC-specific ANAs (Class IIa).
5. Liver biopsy is recommended in AMA-negative patients and/or when associated liver disease is suspected (Class I).
6. Non-invasive methods for staging are under investigation and cannot be routinely recommended, but transient elastography can be used to predict outcome. The role of serial measurements as an endpoint is being evaluated. (Class IIb).

IIIb. PBC: Treatment with ursodeoxycholic acid

1. All patients with PBC and elevated serum ALP should be treated with UDCA 13-15mg/kg/day, even if asymptomatic at presentation (Class I).
2. If use of bile acid sequestrants is necessary for treatment of pruritus, UDCA should be administered 4 hours prior to or after its ingestion (Class I)
3. Response to therapy should be evaluated after 1 year of treatment. This may be done by different approaches (Class IIa).

IIIc. PBC: Treatment of patients with inadequate response to UDCA

1. There is no agreement with regards to the best criteria to determine biochemical response to UDCA. Given costs and ease to use, we suggest using Paris II criteria (FA $\geq 1,5X$ ULN or AST $\geq 1,5X$ ULN or BT >1 mg/dl) (Class IIa).
2. Biochemical response should be evaluated after 1 year of treatment with UDCA to assess prognosis and determine need for adjuvant therapy (Class IIa).
3. Clinicians may use the UK-PBC score or the GLOBE PBC score after 1 year of therapy with UDCA to help determine who needs adjuvant therapy. (Class IIa)
4. There is no consensus with respect to treatment of patients with incomplete response to UDCA. We recommend assessing patients' compliance with therapy and considering alternative or concomitant diagnoses. A liver biopsy may be needed at the hepatologist's discretion. (Class IIa).

5. Budesonide may be considered in patients with PBC, stage I-II and incomplete response to UDCA, especially if there is marked inflammatory activity (Class IIb).
6. Bezafibrate 400mg/day associated with UDCA can be considered as an off-label alternative for patients with PBC and inadequate response to UDCA (Class IIb), but the use of fibrates is discouraged in patients with decompensated liver disease (Child- Pugh-Turcotte B or C) (Class IIa).

V. Pruritus

1. Pruritus is frequently observed in PBC and PSC and tend to decrease in frequency and intensity with disease progression to cirrhosis. (Class I)
2. Treatment of pruritus should be stepwise until resolution or improvement of symptoms using 1st line drugs such as cholestyramine (4-16 g/daily), 2nd line drugs such as rifampicin (150-600 mg/daily), 3rd line drugs such as naltrexone (12.5-50 mg/daily) and fourth line drugs such as sertraline (50-100 mg/daily) (Class I- IIa)
3. The presence of refractory pruritus should be considered in the presence of failure to control itching under maximal doses of cholestyramine, rifampicin, naltrexone and sertraline (Class I)
4. Use of antihistamines and UDCA could not be recommended for treatment of pruritus, with the exception of UDCA in intrahepatic cholestasis of pregnancy (Class I)

5. Due to its effect in pruritus, fibrates may be employed for treatment of pruritus in patients with PBC and PSC (Class IIa)

VI. Fatigue and Hypercholesterolemia

1. Fatigue is frequently seen in cholestatic liver diseases, particularly PBC (Class I)
2. Exclusion of depression, anemia, hypothyroidism and fatigue-inducing drugs should be carried out (Class IIa)
3. There is no approved treatment for fatigue and LT can be eventually considered for severe and incapacitating fatigue, but symptom remission after LT is uncertain (Class IIb)
4. Frequent bed rest, avoidance of sleep deprivation and psychological support are important in the management of fatigue (Class IIa)
5. Hyperlipidemia with high total cholesterol, LDL and HDL-cholesterol is frequently found in subjects with cholestasis, particularly in PBC (Class I)
6. There is no data to support higher risk of atherosclerosis and cardiovascular events in subjects with cholestasis (Class IIb)
7. Statins, when required, are considered safe and effective for treatment of hyperlipidemia in cholestatic liver diseases. (Class IIb)

VII. Osteoporosis and osteopenia

VIII. SPECIAL TOPICS:

VIIIa. Recurrent Cholangitis

1. Patients with recurrent cholangitis due to biliary tract disease refractory or not amenable to medical, endoscopic or surgical treatments should be in waiting list for liver transplantation and receive prioritization (Class I).
2. MELD-exception points should be given to those patients with recurrent cholangitis in the presence of: a) two or more episodes of cholangitis in at least 6 months; b) one episode of recurrent cholangitis with extrahepatic sepsis, severe sepsis or septic shock (not associated with biliary tract procedures) or c) due to infection with multiresistant bacteria (Class IIa).
3. Antibiotic prophylaxis should be given to those patients with PSC or with any other disease associated with biliary obstruction submitted to ERC in order to prevent cholangitis, particularly in the presence of inadequate biliary drainage (Class IIa).

VIIIb. Screening of liver and biliary tract cancer

1. Patients with PSC are at increased risk for hepatobiliary neoplasias, particularly cholangiocarcinoma (CC) and gallbladder cancer (Class I)
2. In the absence of evidence-based data, ultrasound should be performed at least yearly for screening of CC in association with measurement of CA19-9 levels (Class IIb). MRCP should be performed in those patients with suspected CC based on clinical and laboratory

findings. (Class IIb). ERC with brushing cytology or endobiliary biopsies are recommended to establish the diagnosis of biliary tract cancer. (Class IIb).

3. Screening of gallbladder cancer should be performed with yearly ultrasound in subjects with PSC. It is recommended to perform cholecystectomy for all gallbladder polyps in PSC regardless of size. The surgical indication should consider the cost-benefit ratio between the risk of clinical decompensation and the high incidence of gallbladder neoplasia in this population. (Class IIa).
4. Screening for hepatocellular carcinoma should be performed every six months in subjects with cirrhosis due to PSC (Class IIa).

VIIIc. Liver transplantation (LT) for AIH, PBC and PSC

1. Patients with AIH, PSC and PBC, as well as with other should be referred for LT in the presence of complications of portal hypertension and liver failure assessed by the MELD score (Class I)
2. Intractable pruritus and refractory recurrent cholangitis should be considered for prioritization with extra-MELD points in subjects with PBC and PSC (Class I)
3. LT has no role in the management of AIH refractory to treatment in the absence of complications of liver failure and portal hypertension. (Class IIa).
4. LT may be warranted in those patients with decompensation of liver disease due to flares of AIH due to poor adherence or spontaneous disease reactivation. In those cases, drug adjustments should be initially employed with concern due to the higher risk for development

of infection. In the absence of improvement, LT should be considered (Class IIb)

5. Use of prognostic scores for indication of LT for PSC and PBC still deserve better validation. Until now, MELD remains the best score for indication of LT and organ allocation (Class IIa)
6. When LT is considered for AIH, withdrawal or decrease dose of immunosuppressive therapy may be tried when LT appears to be imminent (Class IIb)
7. Maintenance of UDCA in subjects with PSC and PBC in the waiting list for LT is controversial, since its impact in the survival of those patients with end-stage liver disease is probably negligible (Class IIb)
8. In subjects with acute liver failure under suspicion for AIH, after exclusion of other causes of liver disease, even in the absence of autoantibodies, institution of immunosuppressive therapy should be attempted if there is no evidence of active infection. Based on experts' opinion, use of oral or intravenous prednisolone may be attempted, but the dosage still needs to be better established (Class IIa). Treatment should be re-evaluated in five to seven days and corticosteroids should be discontinued in the absence of clinical and laboratory improvement. LT should not be postponed in this setting (Class IIb)
9. Subjects submitted to LT for AIH should receive higher immunosuppression after LT, with two or three drugs. The need for maintenance of low doses of corticosteroids indefinitely is controversial in the literature and should be considered in patients with repeated episodes of acute cellular rejection and in those with a high risk of

disease recurrence after LT, such as: significant inflammatory activity in the explant, high levels of IgG in the immediate pre-transplant, disagreement of HLA-DR3 between donor and recipient (positive receptor/negative donor) (Class IIa).

10. Protocol liver biopsies may increase the diagnosis of AIH recurrence after LT in patients without clinical and biochemical signs of liver disease, but in this setting there is no available data about the benefit of treatment and the decision must be individualized on a case-by-case basis. (Class IIb) Until this date, the role of protocol liver biopsies in PBC and PSC is even less clear and they could not be recommended (Class IIb).
11. Subjects submitted to LT for PBC should receive preferably cyclosporine-based immunosuppression, since the use of tacrolimus has been associated with an increased rate of recurrent PBC (Class IIa)
12. Recurrent PBC is only rarely clinically relevant; there is insufficient data to recommend preemptive usage of UDCA but it appears to improve liver biochemistries and delay histological progression of recurrent disease. The influence of UDCA on the natural history of recurrent PBC still needs to be determined. (Class IIb)
13. Patients with PSC and IBD should undergo annual colonoscopy after LT, due to the increased risk of colonic neoplasia (Class IIa)

Figure 1: Comparison of past and current recommendations for management of autoimmune hepatitis

2015	CURRENT
<p>Autoimmune extrahepatic disorders are frequently seen in patients with AIH. Autoimmune thyroiditis and rheumatoid arthritis are the most common encountered diseases. (Class I)</p>	<p>Autoimmune extrahepatic disorders should be assessed in all subjects with AIH and their first-degree relatives (Class I). AIH in first-degree relatives is very infrequent and family screening is not recommended. (Class I) (4,5)</p>
<p>The diagnosis of AIH should be performed in patients with elevated aminotransferases and gammaglobulin levels, reactivity for SMA, ANA, anti-LKM1, anti-LC1 and anti-SLA and typical histological findings, after the exclusion of other liver disease, particularly viral hepatitis and Wilson's disease (Class I).</p>	<p>In adults, the recommended cut-off titre for autoantibody positivity should be 1:40; for subjects up to the age of 18 years, any level of autoantibody reactivity is infrequent, so that positivity at dilutions below 1:40 could be regarded as clinically relevant (Class I). (6,7)</p>
<p>SMA, ANA, anti-LKM1 and anti-LC1 should be screened by indirect immunofluorescence using rodent tissues, while anti-SLA reactivity should be assessed by ELISA or</p>	<p>Only homogeneous and speckled ANA patterns should be considered as AIH markers. (Class IIa) (6,7)</p> <p>In the presence of anti-LKM1, screening for anti-LC1 antibodies is unnecessary, but if done it must be assessed by techniques with specific</p>

immunoblotting (Class I).

antigens, such as ELISA, immunoblotting or immunodiffusion.

(Class I) (6,7)

If anti-SLA testing is not possible, anti-SSA/Ro seropositivity can be considered an indirect evidence of anti-SLA/LP reactivity. (Class IIa) (8,9)

The revised IAIHSG scoring system and the simplified AIH criteria can be used for the diagnosis of AIH, but the former performs better in the diagnostic evaluation of atypical cases (Class IIa).

For pediatric patients with AIH, it is important to perform MRCP to exclude autoimmune sclerosing cholangitis, which is very common in this age group (Class IIa). (10)

Pathology reports should describe or rule out the presence of the typical histological findings of the disease, such as emperipolesis, interface hepatitis, plasma cells and rosettes of hepatocytes. (Class IIa) (11,12)

In cases of acute presentation of AIH; it's important to distinguish between acute exacerbation of chronic AIH and genuine acute AIH. In the second case, autoantibodies can be

absent, as well as classical characteristics of the disease and liver biopsy shows cirrhosis in 1/3 of cases with frequent zone 3 centrilobular necrosis (Class IIa) (12)

In childhood AIH initial treatment of AIH should be instituted with dual therapy with prednisone 1.5-2 mg/kg/day (up to 60 mg/daily) and azathioprine 1-2 mg/kg/day (Class I)

In childhood AIH, initial treatment of AIH should be instituted with dual therapy with prednisone 2 mg/kg/day (up to 60 mg/day) and azathioprine 1-2.5 mg/kg/day (Class I) (10)

Despite one RCT demonstrating advantages of budesonide over prednisone in the treatment of AIH, the use of budesonide as first-line therapy of AIH in adults, as well as in children cannot up to now be recommended (Class IIb).

Budesonide cannot be routinely recommended as first-line therapy of AIH in adults and children. It could be considered in specific cases, only in patients with early-stage disease with mild-to-moderate fibrosis.(Class IIb). (12)

Clinical, biochemical and histological remission of AIH should be regarded as the primary end-point of treatment (Class I). In order to achieve this primary end-point, treatment should be maintained for at least 24 months.

Treatment should be maintained for at least 36 months. Liver biopsy should be performed at least 24 months after biochemical remission in order to assess histological remission (Class I). (13)

Liver biopsy should be performed at least 18 months after biochemical

remission in order to assess

histological remission (Class I).

Biochemical remission is defined as normalization of aminotransferases and IgG levels. Histological remission is defined as normal histology or minimal hepatitis (periportal activity 0 or 1) or Hepatitis Activity Index < 4 (Class I). (12) The persistence of high titers of ASMA and/or antiactin antibodies in patients with AIH is usually associated with disease activity. (Class IIa) (14)

Close monitoring of AIH patients weaned off immunosuppression is mandatory.

It is recommended to perform liver biopsy to confirm histological remission prior treatment withdrawal (Class I). (12)

Chloroquine monotherapy can enhance biochemical remission and may be offered to patients with AIH after withdrawal of prednisone and azathioprine (Class IIb) (15)

In AIH patients with intolerance to azathioprine or suboptimal responses to dual conventional therapy,

In AIH patients with intolerance to azathioprine, mycophenolate mofetil can be used instead of azathioprine

measurement of azathioprine (Class IIb). (12)

metabolites can be useful to perform drug adjustments as well as to add allopurinol to switch drug metabolism to 6-thioguanine, which is more safe and effective, when compared to azathioprine. Alternatively mycophenolate mofetil can be used in substitution for azathioprine (Class IIb).

Either cyclosporine or tacrolimus may be used in AIH patients without response to conventional treatment, but cyclosporine is usually preferred due to a larger experience with the use of this drug in refractory AIH (Class IIa).

AIH patients with cirrhosis should undergo screening for hepatocellular carcinoma with ultrasound and measurement of alpha-fetoprotein levels every 6 months. (Class IIa)

(12)

AIH per se is not a contraindication to pregnancy nor to breastfeeding. Immunosuppression during pregnancy can be carried out with prednisone and azathioprine, after appropriate discussion with the patient. (12,16) Avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant in breast milk, making this drug an acceptable option for this period (Class IIa). (16,17) Mycophenolate is contraindicated during pregnancy and breastfeeding. (Class I) Prednisone monotherapy is a safer option during pregnancy and breastfeeding. (Class IIb) (16,17) Hepatitis A and B and influenza vaccination should be offered to all AIH patients (Class IIb) (12)

Figure 2: Comparison of past and current recommendations for management of primary sclerosing cholangitis.

2015	Current
<p>Patients under evaluation for cholestasis, in the absence of AMA should be submitted to MRCP (Class Ib)</p>	<p>In addition, ERC can be considered if MRCP and/or liver biopsy is equivocal or contraindicated (Class Ib) (18-19)</p>
<p>IBD should be submitted to colonoscopic screening for colorectal neoplasia (Class Ib).</p>	<p>Colonoscopy should be performed yearly (20-22). In centers with appropriate expertise and resources, consider chromoendoscopy to improve surveillance (20). IgG-4 levels should be measured in subjects with suspected PSC to rule out IgG-4 cholangitis for appropriate management (23)</p>

Figure 3: Comparison of past and current recommendations for endoscopic treatment of primary sclerosing cholangitis.

2015	Current
<p>Before endoscopic treatment, it is mandatory to exclude CC (Class I).</p>	<p>Before endoscopic treatment, it is mandatory to exclude CC (Class I). Concurrent ductal sampling using brush cytology or endobiliary biopsies during ERC is recommended for suspected malignant stricture identified at MRCP (19)</p>
\	<p>Routine administration of prophylactic antibiotics before ERC in patients with PSC is recommended to prevent sepsis and cholangitis (24).</p>

Figure 4: Comparison of past and current recommendations for management of primary biliary cholangitis

2015	Current
<p>AASLD criteria should be adopted for initial evaluation of PBC patients and the diagnosis should be established when 2 of those 3 criteria are met: ALP elevation, presence of AMA, liver biopsy with typical findings</p>	<p>In addition, in the absence of AMA, other PBC-specific autoantibodies: such as sp100 or gp210 are useful for diagnosis (25,26)</p>
<p>Non-invasive methods for staging are under investigation and cannot be routinely recommended</p>	<p>Transient elastography can be used to predict outcome. The role of serial measurements as an endpoint is being evaluated. (27-29)</p>
<p>Response to therapy should be evaluated after 1 year of treatment. This can be done by measuring ALP and bilirubin levels</p>	<p>In addition, Clinicians may use the UK-PBC score or the GLOBE PBC score after 1 year of therapy with UDCA to help determine who needs adjuvant therapy (30,31).</p>
<p>There is no consensus with regard to the best criteria to determine biochemical response to UDCA. Combination of total bilirubin \leq 1 mg/dL and/or ALP \leq 2X ULN was suggested</p>	<p>Use of Paris II criteria (FA \geq1,5X ULN or AST \geq1,5X ULN or BT >1mg/dl) to determine inadequate response to UDCA (32).</p>
<p>There is not enough evidence to</p>	<p>Bezafibrate 400mg/day plus UDCA</p>

support routine use of fibrates or FXR agonists at this time. can be considered an off-label alternative for patients with PBC and inadequate response to UDCA (33,34)

Figure 5: Comparison of the 2015 and current strategies for the management of complications of cholestasis: osteoporosis and osteopenia

2015	Current
<p>Management of bone loss should involve lifestyle changes, physical activity and a well balanced diet rich in calcium and vitamin D. Supplementation of calcium and vitamin D should be considered, independently of BMD results in patients at increased risk for bone loss.</p>	<p>Use of WHO FRAX score is recommended for assessing fracture risk and guide therapy in patients with ALD (35)</p>
<p>Use of bisfosfonates should be considered in the presence of osteoporosis, spontaneous fractures, before and after LT, prolonged use of corticosteroids and chronic cholestasis with T score <-1,5. Alendronate and ibandronate can be employed without distinction, but treatment adherence is better with ibandronate</p>	<p>Supplementation of calcium and vitamin D should be considered in patients with low risk of fractures according to WHO FRAX score</p>
	<p>Supplementation of calcium and vitamin D should be used in association with bifosfonates in patients with moderate/high risk of fractures according to WHO FRAX score (35). Weekly alendronate and monthly ibandronate can be employed without distinction, but</p>

treatment adherence is better with ibandronato (36). Use with caution in subjects with esophageal varices and consider parenteral bifosfonates in the aforementioned patients (25,26,36)

Figure 6: Comparison of the 2015 and current strategies for the screening of liver and biliary tract cancer in primary sclerosing cholangitis

2015	Current
<p>Screening of gallbladder cancer should be performed with yearly ultrasound in subjects with PSC. In the presence of polyps of any size or any other lesions, cholecystectomy should be performed (Class IIa)</p>	<p>Screening of gallbladder cancer should be performed with yearly ultrasound in subjects with PSC. It is recommended to perform cholecystectomy for all gallbladder lesions in PSC regardless of size. The surgical indication should consider the cost-benefit ratio between the risk of clinical decompensation and the high incidence of neoplasia in this population (Class IIa). (20,22)</p>

Figure 7: Comparison of the 2015 and current strategies for the management of liver transplantation (LT) for autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis

2015	Current
<p>In subjects with acute liver failure, after exclusion of other causes of liver disease, even in the absence of autoantibodies, institution of immunosuppressive therapy should be attempted in subjects under suspicion for AIH (Class IIa). Treatment should be evaluated after 5 to 7 days and may not postpone LT, when indicated (Class IIb)</p>	<p>In severe acute hepatitis, even in the absence of pathognomonic markers or IAIHG diagnostic criteria, treatment with corticosteroids should be considered if there is no evidence of active infection. Use of oral or intravenous prednisolone may be attempted, but the dosage still needs to be better established (Class IIa). Treatment should be re-evaluated in five to seven days and LT should not be postponed in this setting (Class IIb) (12, 37-39)</p>
<p>Subjects submitted to LT for AIH should receive higher immunosuppression, but there is no consensus about the requirement of corticosteroids indefinitely in the long-term (Class IIa).</p>	<p>Subjects submitted to LT for AIH should receive higher immunosuppression after LT. The need for maintenance of low doses of corticosteroids indefinitely is controversial in the literature and should be considered in patients with repeated episodes of acute cellular</p>

rejection and in those with a high risk of disease recurrence after LT, such as: significant inflammatory activity in the explant, high levels of IgG in the immediate pre-transplant, disagreement of HLA-DR3 between donor and recipient (positive receptor/negative donor) (Class IIa). (40)

Subjects submitted to LT for PBC should receive preferably cyclosporine-based immunosuppression. Recurrent PBC is only rarely clinically relevant; there is insufficient data to recommend preemptive usage of UDCA but it appears to improve liver biochemistries and delay histological progression of recurrent disease. The influence of UDCA on the natural history of recurrent PBC still needs to be determined. (41,42)

The indication of liver transplantation due to fatigue in CBP is still controversial, since fatigue does not

disappear in most cases after LT
(Class IIa) (25,41)

Patients with PSC and IBD should
undergo annual colonoscopy after LT,
due to the increased risk of colonic
neoplasia (Class IIa) (43,44)

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