Consensus

Chinese Expert Consensus for the Diagnosis and Treatment of Cholestatic Liver Disease

Chinese Expert Committee on the Diagnosis and Treatment of Cholestatic Liver Disease

Cholestatic liver disease (CLD) is a common problem in clinical practice with the main manifestation being cholestasis. Recently, there has been a steady increase in knowledge associated with the diagnosis and treatment of CLD. Therefore, the experts in China were organized by the editorial board of Chinese Journal of Experimental and Clinical Infectious Diseases (Electronic Edition), Chinese Journal of Liver Diseases (Electronic Edition) and Infection International (Electronic Edition) to collect and analyze relevant research, ultimately resulting in the development of this work (Chinese Expert consensus for the diagnosis and treatment of CLDs, also abbreviated as consensus).

This document describes the latest research findings for the diagnosis and treatment of CLD according to the principles of evidence-based medicine. The evidence level is listed in Table 1. All experts concur that this work represents a reference for the diagnosis and treatment of CLD, which is influenced by many factors. Therefore, a combination of standardized and personalized treatments may produce the optimal therapeutic effect. This expert committee will update the corresponding content to include accumulating clinical evidence for consensus in the diagnosis and treatment of CLD.

DEFINITION, CLASSIFICATION AND DIAGNOSIS PROCEDURE FOR CLD

Definition

CLD is a common liver disease that results from impaired bile formation and secretion or abnormal biliary excretion.¹ It can be classified as hepatocellular cholestasis, bile ductular cholestasis and mixed cholestasis based on different etiology. Cholestasis symptoms manifested for longer than six months are diagnosed as chronic cholestasis. Biochemically, patients can be diagnosed with CLD if alkaline phosphatase (AKP) levels exceed 1.5 times the upper

limit of the normal (ULN) and γ -transpeptidase (γ GT) levels exceed 3 times ULN.

Common etiology classification of adult CLD (Table 2)²

Diagnosis procedure^{3,4}

Suspected cholestasis should be diagnosed according to the following steps (see Figure 1):

History inquiry

Inquiry should include previous history, family history, medical history and alcohol intake.

Physical examination

Abdominal ultrasound examination and computed tomography (CT) scan

These are used to exclude extrahepatic bile duct obstruction. Endoscopic ultrasonography (EUS) is performed to evaluate distal obstruction of the biliary tract if necessary.

Magnetic resonance cholangiopancreatography

This is performed for unexplained CLD patients. Endoscopic retrograde cholangiopancreatography (ERCP) should be performed in highly selective cases. MRCP or EUS should be given priority to ERCP if no requirement for treatment is expected. This is due to the relatively higher incidence of complications and mortality associated with ERCP.

Laboratory examinations

These should include liver function, viral serological diagnosis and autoantibody screening. Liver biopsy should be performed in cases of unexplained intrahepatic cholestasis or in antimitochondrial antibodies (AMA) negative patients.

Recommendations

Detailed history and physical examination is crucial (III).

Ultrasound and CT are first-line non-invasive imaging methods for identifying intrahepatic and extrahepatic cholestasis (III).

Serum AMA testing is essential for chronic intrahepatic cholestasis (III).

MRCP, EUS, ERCP, and liver biopsy should be considered for further detection (II).

Institute of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, No. 8 Jingshun East Street, Chaoyang District, Beijing 100015, China

Correspondence: Jun Cheng, E-mail: jun.cheng.ditan@gmail.com

Table 1. Level of evidence criteria

Levels of evidence	Criteria
I	Evidence from meta-analysis or multiple randomized, controlled trial
II	Evidence from single randomized trial or well-designed clinical trial, without randomization
III	Evidence from case report or opinions of respected authorities

Table 2. Common etiology classification of adult CLD

Hepatocellular cholestasis	Bile ductular cholestasis
Septicopyemia and endotoxemia	Primary biliary cirrhosis (PBC)
Virus hepatitis	Primary sclerosing cholangitis (PSC)
Alcohol or nonalcoholic fatty liver disease	PBC, PSC and autoimmune hepatitis (AIH) overlap syndrome
Drug or parenteral nutrition-associated cholestasis	IgG4 related cholangitis
Hereditary disease: Benign recurrent intrahepatic cholestasis (BRIC)	Idiopathic adulthood ductopenia
Progressive familial intrahepatic cholestasis (PFIC)	ductal plate malformation (DPM): bile duct hamartomas, Caroli's syndrome
ABCB4 gene deficiency	Cystic fibrosis
Intrahepatic cholestasis of pregnancy (ICP)	Drug-induced bile duct disease
Erythropoietic protoporphyria	Graft versus host disease
Malignant infiltration disease: hemopathy and metastatic carcinoma	Secondary sclerosing cholangitis: various cholangiolithiasis, ischemic bile duct disease (hereditary hemorrhagic telangiectasia, polyarteritis nodosa and other aneities), acquired immune deficiency syndrome (AIDS) and other immunosuppression-related infectious cholangitis
Benign infiltration disease: amyloidosis	
liver sarcoidosis and other	
granulomatosis, glycogen storage disease	
Paraneoplastic syndrome: Hodgkin disease and kidney cancer	
Ductal plate malformation: congenital hepatic fibrosis	
Nodular regenerative hyperplasia	
Angiopathy: Budd-Chiari syndrome	
veto-occlusive disease, and congestive liver disease	
Cirrhosis (any reason)	

THE TREATMENT OF CLD

Etiological treatment

Specific treatment strategies should be designed for CLD with different etiology.

Symptomatic treatment

Ursodeoxycholic acid (UDCA)

Most CLD patients can be treated by UDCA administration. UDCA stimulates excretion of endogenous bile acid (BA)⁵ alters BA composition and increases the ratio of hydrophilic BA. These effects may protect hepatocytes and cholangiocytes against the toxic effects of endogenous BAs, prevent hydrophobic BA-induced mitochondrial membrane damage, inhibit liver cell apoptosis, significantly improve serum function and simultaneous liver histological features, slow further progression into hepatic fibrosis, cirrhosis, and esophageal varices and ultimately prolong the survival time in patients with CLD.

Glucocorticoids and other immunosuppressors

Glucocorticoids limit the activation of T lymphocyte through reducing the production of proinflammatory

cytokines and expression of cell adhesion molecules, and selectively inhibit antibody production by B lymphocytes.² In vivo, azathioprine is slowly transformed by the liver into mercaptopurine, which acts as a purine antagonist that interferes with DNA synthesis and inhibits lymphocyte proliferation.² Low doses of mercaptopurine have an inhibitory effect on cellular immunity. In some CLD patients, combination therapy comprising azathioprine and reduced glucocorticoid doses can be effective in enhancing the therapeutic effects and decreasing adverse reactions.

S-adenosyl-L-methionine (SAME)

SAME is a naturally-occurring, physiologically-active substance present in human tissues, which is synthesized by SAME synzyme from ATP and methionine. Through transmethylation, SAME increases the membrane phospholipid content, membrane fluidity and Na⁺-K⁺ATP enzyme activity resulting in acceleration of BA transport in the liver.⁶ Also through transmethylation, SAME increases the production of glutathione and cysteine in liver cells leading to improved detoxification and protection against free radical damage. Furthermore, the generated taurine

Figure 1. Diagnosis procedure for adult CLD.

detoxification also combines with BA to increase its solubility, which has some effect on the prevention of intrahepatic cholestasis.

ERCP and endoscope-assisted treatment

Diagnostic ERCP has been regarded as a standard option for suspected PSC.⁷ Complications are very rare when only diagnostic ERCP is performed. However, the rate of complications increases to more than 14% when endoscope-assisted intervention is conducted. Such complications include sacculus expansion, endoscopic papillotomy and stent implantation.⁷

Liver transplantation

Liver transplantation significantly improves the survival of patients with advanced CLD.^{8,9} The indications for transplantation in CLD are similar to those associated with hepatic failure for other reasons.

Liver transplantation may be indicated when the quality of life is intolerable in decompensated cirrhotic patients or when the life expectancy of patients is less than one year due to refractory ascites, spontaneous bacterial peritonitis, repeated variceal bleeding, hepatic encephalopathy or hepatocellular carcinoma.

Blood purification

Autoantibodies and immune complexes are present in CLD to varying degrees that may be associated with CLD development and progression. In addition, cholestasis may contribute to some substance deposition in vivo, pruritus symptoms and even secondary injury to the nervous system, heart and kidney. Blood purification techniques can be used to eliminate these pathogenic and harmful substances, possibly improving the condition of the patient or

providing symptom relief. The most common methods of artificial liver support for CLD in current use include plasma exchange (PE), PSH and molecular adsorbent recycling systems (MARS). These techniques are applied on the development of severe jaundice or pruritus in CLD patients.

Pruritus is one of the most common symptoms of intrahepatic cholestasis. Severe pruritus has a considerable effect on the quality of life in patients. However, the mechanism underlying the development of pruritus is unclear. It is postulated to be related to the accumulation of substances due to cholestasis which influence normal nerve conduction. Therefore, PE, PSH and MARS pruritus should be taken into account in unresponsive patients or those with contraindications to pharmacotherapy (III).¹⁰⁻¹³

Although PE removes circulating autoantibodies and immune complexes, there is no evidence that PE improves the course and prognosis of autoantibody-related CLD. In CLD patients with severe jaundice or hepatic failure, non-biologic or biologic artificial liver support systems can be selected to remit disease progress or as a transitional treatment for liver transplantation (III).¹⁴

Traditional Chinese medicine and other treatments

Cholestatic hepatitis belongs to the group of jaundice diseases in Traditional Chinese medicine. The summarized pathogenesis characteristics are endoretenion of damp heat, middle burner, suffocating in liver and gall bladder, liver dysfunction and bile overflow. The disease is primarily located in the liver and gall bladder, spleen and stomach and even the kidney in chronic disease. The main therapeutic methods include clearing heat and promoting diuresis, activating blood and dissolving stasis, cooling the blood and reducing phlegm according to the principles of treatment based on syndrome differentiation.

Galle-Donau is a compound preparation of alpha-naphthylacetic acid and methyl benzyl alcohol nicotinate that has a capability to stimulate physiologic choleresis in the aqueous or solid phase.¹⁵ Furthermore, Galle-Donau shows significant effects on anti-inflammatory regulation. For example, Galle-Donau relieves inflammatory edema in the portal area and bile capillaries, resulting in improved intrahepatic cholestasis.

COMMON TREATMENTS FOR CLD

PBC

Usually, PBC patients present with fatigue, pruritus and jaundice as the major manifestations. Therefore, the key marker for diagnosis of PBC is AMA, with a positive percentage of more than 90%. Furthermore, the specificity of AMA for the diagnosis of PBC

can exceed 95%. AMA is determined by indirect immunofluorescence, with titer $\geq 1:40$ considered as positive reactions. Due to differences in methodology, the lowest dilution for the detection of positive reactions is 1:100 in most liver disease research centers in China. However, further studies are essential to evaluate the generation false negative results at this dilution. If possible, AMA anti-M2 subtype (anti-PDC-E2) should be used as another effective measurement indicator. Non-specific AMA in serum are detected in at least 30% of PBC patients.³

In adult patients, PBC can be diagnosed when unexplained AFP increases and AMA ($\geq 1:100$) and anti-PDC-E2 antibodies emerge. Liver biopsy seems to be non-essential for these patients, but can be used for evaluating the disease activity and staging (III). However, if specific antibodies are absent, liver biopsy is an indispensable method for the diagnosis of PBC. Also, if inappropriate serum transaminase and IgG levels increase, liver biopsy is helpful in distinguishing additional and other diseases (III). The population with positive AMA but normal liver serology should be followed up annually and examined repeatedly for CLD-related biochemical markers (III).

Treatment for PBC

UDCA

Long-term studies suggest that administration of UDCA at a dose of 13-15 mg•kg⁻¹•day⁻¹ may be justified for treatment of PBC patients because significant improvement in the long-term survival of these patients has treated with UDCA has been observed for 10-30 years (see Table 3).¹⁶⁻¹⁹

Corticosteroid and other immunosuppressors

Prednisolone improves the serological and histologic index in the liver. However, it may elicit a significant decrease in bone mineral density, which limits its prolonged usage in PBC patients.² Other immunosuppressors, such as azathioprine and cyclosporine are also not recommended for standard PBC treatment.²

Liver transplantation

Liver transplantation can significantly improve survival time in advanced PBC patients.^{8,9} The indications of transplantation are similar to those in hepatic failure due to other reasons. Liver transplantation may be indicated when the quality of life is intolerable in decompensated cirrhotic patients or when the life expectancy of patients is less than one year due to refractory ascites, spontaneous bacterial peritonitis, repeated variceal bleeding, hepatic encephalopathy or hepatocellular carcinoma. Liver transplantation can be considered when PBC patients present with the following symptoms: serum bilirubin content of 6 mg/dl (103 μ mol/L), Model for End-stage Liver Disease (MELD) score >12 ,²⁰ intolerable pruritus or frequent

Table 3. A prospective cohort study on the effect of UDCA treatment on long-term survival of PBC patients

Reference	Patient numbers	UDCA dose	Follow-up time	Population	Survival rate of non-transplantation patients	
					Prospective survival rate compared with the healthy control	Prospective survival rate compared with that calculated by Mayo model
16	262	13-15 mg•kg ⁻¹ •d ⁻¹	Average time: 8 years (range, 1-22)	Total Layering	Histological grade: 1-2 NS (<i>P</i> = 0.1) NS (<i>P</i> = 0.5)	<i>P</i> < 0.01 <i>P</i> < 0.001
17	297	unknown	Median time: 68 months (range, 3-126)	Total Layering	Histological grade: 3-4 Normal TBil and ALB Normal TBil but abnormal ALB <i>P</i> < 0.05 <i>P</i> = 0.0003 NS (<i>P</i> = 0.9) <i>P</i> < 0.00001	NS (<i>P</i> = 0.5) <i>P</i> = 0.01 <i>P</i> = 0.005 NS (<i>P</i> = 0.43)
18	192	15 mg•kg ⁻¹ •d ⁻¹	Average time: 6.8 years Median time: 7.5 years (range, 1.5-14.3)	Total Layering	With biochemical response ^a Without biochemical response ^a <i>P</i> < 0.001 NS (<i>P</i> = 0.15) <i>P</i> < 0.001	<i>P</i> < 0.001 <i>P</i> < 0.001
19	292	13-15 mg•kg ⁻¹ •d ⁻¹	Average time: 6.1 years Median time: 5.3 years (range, 1.2-21.5)	Total Layering	With biochemical response ^b Without biochemical response ^b <i>P</i> < 0.0001 NS (<i>P</i> = 0.8) <i>P</i> < 0.0001	<i>P</i> = 0.01 <i>P</i> < 0.0001 NS (<i>P</i> = 0.9)

Notes: Standard for "Good biochemical response" to UDCA

^a: "Barcelona" standard¹⁸: AKP content decreased by 40% or return to normal after one year treatment

^b: "Paris" standard¹⁹: Serum bilirubin ≤ 1 mg/dl (17 μmol/L), AKP ≤ 3 times ULN and AST ≤ 2 times ULN after one year treatment

fractures due to osteoporosis.

Recommendations

UDCA should be administrated at a dosage of 13-15 mg•kg⁻¹•d⁻¹ (I) for PBC patients, including chronic asymptomatic patients (II).

Long-term effects of UDCA can be observed in early stage patients or those with good biochemical responses (II). These biochemical responses should be estimated after one year of treatment.

There is still lack of consensus on how to treat the patients with poor biochemical responses (III).

Liver transplantation can be indicated in advanced patients presenting with serum bilirubin content exceeding 6 mg/dl (103 μmol/L), decompensated cirrhotic patients with an intolerable quality of life or patients with a life expectancy less than one year due to refractory ascites, spontaneous bacterial peritonitis, repeated variceal bleeding, hepatic encephalopathy or hepatocellular carcinoma (II).

PBC-AIH Overlap Syndrome

Diagnosis of PBC-AIH overlap syndrome

Overlap syndrome is a commonly used descriptive nomenclature in liver disease. The criteria for diagnosis of PBC-AIH overlap syndrome are listed in Table 4.²¹

Treatment of PBC-AIH overlap syndrome

The treatment recommendations for PBC-AIH overlap syndrome are obtained from the results of retrospective or non-randomized studies. Simultaneous administration of UDCA and immunosuppressors in PBC-AIH overlap syndrome patients is controversial.²² A retrospective cohort study indicated that the biochemical response and survival rate after UDCA

treatment for 24 weeks in 12 cases of PBC-AIH Overlap Syndrome was similar to that observed in 159 cases of PBC without AIH.²¹

Furthermore, Chazouillères et al²³ reported 17 cases of PBC-AIH overlap syndrome were divided into two groups that received UDCA + immunosuppressors or UDCA treatment alone (follow-up 7.5 years). Their results showed that biochemical responses in terms of AIH features (ALT < 2 × ULN and IgG < 16 g/L) were achieved in four of six patients and fibrosis did not progress in the UDCA + immunosuppressors group. However, in the UDCA treatment alone group, biochemical responses were only observed in three of eleven patients, whereas the remaining eight patients were non-responders with increased fibrosis in four patients. These data suggest that a combination of glucocorticoid and UDCA may be the optimal therapeutic schedule for most diagnosed PBC-AIH Overlap Syndrome patients. An alternative therapeutic schedule consists of treatment with UDCA alone followed by administration of glucocorticoids in the absence of an ideal biochemical response after three months.²³ The initial dosage of prednisone is 0.5 mg•kg⁻¹•day⁻¹ and this dose is be gradually reduced when decreased levels of glutamic-pyruvic transaminase are detected. The course of treatment is longer than six months.

Other immunosuppressors, such as azathioprine, have also been demonstrated as an attractive alternative to glucocorticoids in the treatment of AIH patients. However, no data exists on their use in PBC-AIH overlap syndrome patients. In addition, a therapeutic effect of cyclosporine A has been reported in corticosteroid-resistant patients.²⁴ Immunosuppressors appear to be indispensable when

Table 4. Diagnostic criteria for PBC-AIH overlap syndrome

PBC diagnosis criteria	AIH diagnosis criteria
AP > 2 × ULN or γGT > 5 × ULN	ALT > 5 × ULN
AMA ≥ 1 : 100	IgG > 2 × ULN or positive anti-smooth muscle antibody (ASMA)
Moderate or severe bile duct damage in liver biopsy	Moderate or severe periportal inflammation or lymphocytes and classic necrosis in liver biopsy

Notes: Patients can be diagnosed with PBC-AIH overlap syndrome when they meet two or more above criteria. In addition, AMA negative PBC-AIH overlap syndrome should be considered.

AIH occurs simultaneously with UDCA treatment (that is, sequential overlap).²⁵

Recommendations

A simple gold standard for the diagnosis of PBC-AIH overlap syndrome is lacking. Only some can be regarded as reference (II);

Once the patient is diagnosed with PBC, PBC-AIH Overlap Syndrome should not be disregarded as this may have an important effect on treatment strategies (II).

A combination of glucocorticoids and UDCA is the recommended therapeutic schedule for PBC-AIH Overlap Syndrome patients (II), another alternative options are that patients should be treated initially with UDCA only followed by administration of glucocorticoids in the absence of an ideal biochemical response after a period of time (such as three months) (II). In patients requiring very long-term therapy, a lower dosage of steroid should be considered (III).

PSC

Diagnosis of PSC

PSC is a chronic form of CLD characterized by inflammation and fibrosis in the intrahepatic and extrahepatic bile ducts. This disease may lead to irregular biliary tract damage, including multisite stenosis. Furthermore, it is a progressive disease, ultimately leading to cirrhosis and liver failure.

Although the etiology of PSC is unknown, there is evidence of genetic predisposition. The ratio of males to females is 2:1 and children and the aged are at risk of this disease. The average age of patients is 40 years. More than 80% of patients with PSC also have inflammatory bowel disease (IBD), usually ulcerative colitis (UC). Therefore, a typical PSC patient is a young or middle-aged man with the biochemical and clinical features of CLD and IBD.

The patient can be diagnosed with PSC only if all of the following criteria are met: serological markers of cholestasis (such as AKP and γGT) are increased and cannot be alternatively accounted for and MRCP or ERCP indicates characteristic bile duct changes, including multiple stenosis and segmental dilatation.²⁶ If presented with clinical, biochemical and histologic features of PSC, but normal cholecystography, some patients are classified with “ductular PSC” (especially associated with IBD) or “Proteus syndrome”. In

addition, secondary or other cholestatic diseases should be exclusive.

Treatment of PSC

UDCA

UDCA is an effective medicine for the treatment of PBC and therefore, it is recommended as a candidate drug for PSC.²⁷ In the early 1990s, one study demonstrated improvement in the biochemistry and histology of partial PSC cases following UDCA administration at a dosage of 10-15 mg•kg⁻¹•day⁻¹. In 1997, Lindor et al² enrolled 105 patients with well-documented PSC in a randomized, double-blind study comparing UDCA (13-15 mg/kg) with placebo. The results showed that UDCA, but not placebo, was associated with improvement in serum alkaline phosphatase, aspartate aminotransferase, bilirubin, and albumin levels after two years of follow-up. However, UDCA was not associated with significant changes in histologic findings in the liver or changes in symptoms based on a grading system. Further, a total of 219 randomized patients received 17-23 mg•kg⁻¹•day⁻¹ of UDCA or placebo for 5 years in Scandinavia.²⁷ The results showed that the survival rate of PSC patients was significantly improved in the UDCA group compared with that in the placebo group. However, no significant difference was detected compared with previously administered UDCA at a lower dose. Biochemical responses were also relatively poor compared with those observed in other studies, suggesting poor compliance in some populations. Recently, a multicenter study of 150 patients has failed because UDCA at a higher dose 28-30 mg•kg⁻¹•day⁻¹ increases the risk of progressive disease reaching the primary end point, including liver transplantation and phlebeurysma, despite causing improvement in biochemical characteristics.²⁸⁻³⁰ Thus, the role of UDCA in reducing the progression of PSC-related liver diseases is still unclear. A higher dose of UDCA may be harmful in advanced disease.

Immunosuppressors and other preparations

There is no evidence that glucocorticoids and other immunosuppressors play an important role in the activity or outcome of PSC, although the roles of several immunosuppressors including prednisone, budesonide, azathioprine, cyclosporine A, methotrexate, tacrolimus, pentoxifylline, colchicin, and penicillamine, have been explored in a randomized,

placebo-controlled study. Therefore, these agents are not recommended for the treatment of PSC.

ERCP and endoscope-assisted therapy

Diagnostic ERCP has been regarded as a standard option for suspected PSC.⁷ However, the rate of complications, such as sacculus expansion, endoscopic papillotomy and stent implantation, increases to more than 14% when endoscope-assisted intervention is conducted.

Animal and human studies have shown that endoscope-assisted therapy of biliary structures improves the biochemical index of the liver, pruritus symptoms, and decreases the risk of the recurrence of cholecystitis. Therefore, symptomatic patients can be allowed to receive repeated endoscope-assisted dilatation therapy in the main bile duct.

Liver transplantation

Liver transplantation is the sole option for the treatment of end-stage PSC patients and can cure progressive disease. In experienced centers, the survival rate of one year and ten years after liver transplantation is 90% and 80%, respectively.

Recommendations

Extensive data shows UDCA (15-20 mg/d) improves the serologic index or other alternative prognostic indexes (I), but has no effect on survival rate (II). However, UDCA is not particularly recommended as a common therapeutic drug for PSC based on these limited data. Glucocorticoids and other immunosuppressors are not recommended for the treatment of adult PSC, unless bearing evidence of Overlap Syndrome (II). Bile duct dilatation therapy is indicated when overt biliary structures are accompanied by obvious cholestasis (II). Liver transplantation could be introduced for end-stage PSC patients (II) and patients with atypical hyperplasia in cases of cholangiocytes or severe recurrent bacterial cholangitis (II).

Intrahepatic cholestasis of pregnancy (ICP)

ICP, also known as obstetric cholestasis (OC), is a pregnancy-specific disorder, which manifests in the latter half of pregnancy as pruritus, elevated serum aminotransferases and BA levels, with spontaneous relief of signs and symptoms after delivery.³¹ The etiology of ICP is complex and not fully understood. There is considerable geographical variation in the incidence of ICP, with morbidity of 6.5% to 15.6% in Chile and South Africa (global high-risk areas), 1% to 4% in Yangtze river basins, China (Asian high-risk areas), 0.4% to 2.0% in Europe (Northern Europe high-risk areas: Gulf of Bothnia, Baltic Sea) and 0.2% to 0.8% in Australia. ICP disappears after parturition, with a good prognosis for pregnant woman. However, ICP can easily induce fetal distress, premature birth

and perinatal death. With the development of improved pregnancy and newborn care, perinatal mortality has been significantly reduced, approximately close to whole population.³³

Diagnosis

Women presenting with the main symptom of pruritus during pregnancy, can be diagnosed with ICP after excluding other skin and liver diseases. Liver function tests are essential in all such cases. ICP diagnosis should be considered in cases of pruritus of unknown etiology, with mild to moderate increases in aminotransferases and BA levels ($>10 \mu\text{mol/L}$).³⁴ In addition, ICP is also accompanied by mild jaundice and liposoluble dyspepsia. Pregnancy may be the sole cause of pruritus and abnormal biochemical indexes. The symptoms, sign and abnormal biochemical indexes rapidly disappear or return to normal postpartum. Ten days after delivery, liver function and BA levels are reviewed. If abnormal liver function is still present at six months postpartum, priority should be given to other chronic liver diseases, such as PBC, PSC and chronic hepatitis, all of which are characterized by pruritus in the latter half of pregnancy.

The diagnosis of ICP requires the exclusion of other skin and hepatobiliary system conditions and follow-up visits postpartum. The diseases for exclusion include autoimmune chronic active liver disease and liver damage due to hepatitis virus, Epstein-Barr virus, cytomegalovirus and ABCB4 deficiency.³⁵ Ultrasonic testing is conducive to rule out other serious liver diseases and hepatolithiasis. The patient's condition should be evaluated every one to two weeks. ICP is not associated with deviation of alanine aminotransferase (ALT) and serum bilirubin levels $< 170 \mu\text{mol/L}$ (10 mg/dl) and normal coagulation function. There is no clear relationship between the degree of ICP symptoms and abnormal biochemical indexes, and fetal death. Thus, termination of pregnancy should not depend on abnormal biochemical indexes. However, the prognosis of the fetus is indicated to be related to the duration of pruritus and serum BA levels in clinical studies. Levels of BA $>40 \mu\text{mol/L}$, and alanine aminotransferase (ALT) $>200 \text{ U/L}$ indicate adverse fetal outcome.³⁴ Perinatal risk factors are evaluated by the following algorithm: $\text{BA} \times \text{exposed time/gestational age}$.

Pharmacotherapy

UDCA

UDCA is classified as a category B drug for pregnancy by US FDA, that can be used for treatment of ICP patients during the second or third trimester,³⁶ without obvious adverse reactions either the mother or the fetus.³⁷ UDCA at a dose of $10\text{-}20 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ has been demonstrated as the first-line treatment in ICP patients through a 8-week randomized, controlled study.³⁸ Pruritus and liver function were improved in

67% to 80% of ICP patients. However, it is unclear whether UDCA reduces the antenatal complications because a recent study has indicated the incidences of antenatal complications were decreased in both the placebo and UDCA groups. Although UDCA is not approved for use in the breast-feeding period, it may be safe for neonatus because active constituent of UDCA is not found in breast milk. UDCA should not be administered in the first three months of pregnancy.

SAMe

If pruritus is not been significantly improved after UDCA administration for several days, a higher dose of UDCA ($25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) or SAMe can be applied.^{39,40} SAMe has been approved by the SFDA to use in the treatment of ICP.

Corticosteroids

The use of prednisone at a low dose in pregnancy and lactation period is safe, although administration of prednisone in the first three months of pregnancy increases the risk of cleft lip in the fetus. Furthermore, increased risk of premature rupture of membranes and hypoadrenia are also reported in cases of organ transplantation.³⁷ Hexadecadrol (12 mg/day) exerts a therapeutic effect on ICP when administered at a dose of 12 mg/day for seven days, followed by a gradually decreasing the dose, and drug withdrawal after ten days. Considering the harmful effects on the fetus and neonatus, hexadecadrol are not recommended as the optimal treatment of choice for ICP. Thirty-five weeks before pregnancy, glucocorticoids are essential to promote the development of the fetal lung.

Azathioprine

Although teratogenesis is indicated in some animal studies, it is believed that azathioprine is safe for usage in pregnancy. Treatment experiences have accumulated due to the wide application of azathioprine in female AIH patients, rheumatic arthritis, IBD and organ transplantation. In addition, the benefits and risks should be fully evaluated prior to treatment. Azathioprine is present in breast milk, albeit at low levels.⁴¹

When the drug is used to promote biliary excretion, magnesium sulfate, ristodrine and calcium channel blockers are also necessary to prevent premature birth and to promote fetal growth and lung development. Vitamin K1 can be administered to prevent bleeding in

the mother and fetus.

Advances in fetal monitoring and the uptake of the opportunity of pregnancy termination have had great significance on the reduction of perinatal mortality. At week 35, pregnancy should be terminated on the occurrence of untamed progressive disease and contractions, abnormal quickening, absent fetal heart rate variability, negative stress test response, and meconium-stained amniotic fluid. Fetal anoxia is not detected when disease remains stable and fetal monitoring is strengthened.

Safety assessment of drugs for CLD in pregnancy

The disease will not progress when the patients present with the mild condition or static CLD during the pregnancy and child birth. However, changes may be present in patients with AIH or Overlap Syndrome. Thus, prednisone $\pm$ azathioprine should continue to be administered for AIH patients during pregnancy to prevent recurrent disease which may confer greater risk than that associated with these drugs. A summary of the safety assessment of the drugs for CLD is shown in Table 5.⁴²

Recommendations

Defining characteristics of ICP

A, Pruritus in gestation period; B, elevated serum ALT and BA; C, ruling out other diseases that also result in abnormal liver function and pruritus (II). Recovery of liver function postpartum could be conducive to ICP diagnosis.

Incidence of premature birth

This increases in ICP patients (idiopathic or iatrogenic) (II). There is lack of detailed recommendations for fetal monitoring (III). UDCA can alleviate pruritus symptoms and improve liver function (I), but there is insufficient evidence to support its use in decreasing fetal complications (II).

For patients in the second or third trimester of pregnancy

UDCA can be applied for symptomatic patients in the second or third trimester of pregnancy (I).

For AIH patients during pregnancy

Administration of prednisone $\pm$ azathioprine should be continued for AIH patients during pregnancy to prevent recurrent disease which may confer greater risk than that associated with these drugs (III).

Table 5. Safety assessment of the drugs for CLD

Drugs	Harm to fetus (FDA grade)	Security of use
UDCA	B	Low risk
Prednisolone	C	Low risk: increase the risk of harelip and hypoadrenia
Azathioprine	D	Low risk

Notes: Classification of harm to fetus (FDA): A: no risk; B: risk in animal experiment, but not in human; C: not exclusive harm to the human; D: harm to fetus; X: Absolute contraindication

Drug-induced CLD

Drugs are a common cause of hepatocellular cholestasis. Drug-induced liver damage includes hepatocellular damage, cholestasis or mixed type. Of these, approximately 20% to 25% are cholestasis type, with characteristic AKP $>2 \times$ ULN or R value (the ratio between ALT/ULN and AKP/ULN) ≤ 2 .⁴³

Drugs can evoke almost all types of liver damage.⁴⁴ Common drugs known to induce CLD comprise angiotensin converting enzyme inhibitors, amoxicillin/clavulanic acid, wintermin, chlorpromazine, erythrocine and Chinese herbal medicines.

Due to the insidious onset of drug-induced CLD, the time of drug administration is usually more than one month. The clinical manifestations consist of jaundice, rash and symptoms of liver parenchymal injury, such as anorexia, fatigue and discomfort, epigastric pain, pruritus, right upper abdominal tenderness and hepatomegaly. Of these pruritus is the most specific symptom of CLD, present in 20% to 50% of jaundice patients.

Laboratory examination is characterized by elevated AKP, γ GT and other bile duct injury indexes, such as BA and aminotransferase, with negative virus labeling and AMA.

The key to treatment is withdrawal of the drug responsible for the induction of liver damage and avoidance of the administration of alternative medication of the same biochemical family which will result in the risk of cross-toxicity between the drugs due to the same chemical structure. In addition, rapid elimination of the drug is essential.

Santini et al⁴⁵ reported that the biochemical index in 50 patients with drug-induced liver damage was significantly improved after treatment with SAME. A randomized, double-blind study of 72 patients reported hepatotoxicity and cholestasis in 15 of 36 patients treated with cyclosporin alone, whereas no cases of liver cytotoxicity were observed in the group treated with cyclosporin in combination with ademetionine.⁴⁶ Cortical hormones can be considered in drug-induced CLD, particular in patients with high immune sensitivity although the occurrence of adverse effects should be closely monitored.² In patients with poor responses to drugs and a protracted course of disease, artificial liver support should be introduced.⁴⁷

Recommendations

Drugs can induce almost all types of liver damage. Approximately 20% to 25% of cases are of the cholestasis type, with characteristic AKP $>2 \times$ ULN or $R \leq 2$.

The prognosis is relatively good (I).

The key to treatment of drug inducing liver damage is withdrawal and elimination and avoidance of alternative medication of the same biochemical family.

Most patients gradually recover after drug withdrawal (III).

SAME, UDCA, and antioxidants (such as reduced glutathione) can be selected for therapeutic intervention (II). In immune-mediated CLD, cortical hormones can be considered (III).

All types of viral hepatitis-induced CLD

All types of viral hepatitis (acute and chronic) can cause cholestatic hepatitis. HBV- and HEV- induced acute cholestatic hepatitis is more common, with similar clinical manifestations of acute icteric hepatitis, such as fever, loss of appetite, nausea and acratia. In addition, as the symptoms are alleviated and jaundice increases, patients exhibit pruritus, grey feces and direct bilirubin (accounting for 60% of the total bilirubin), elevated AKP and γ GT and positive virus markers.

Chronic cholestatic hepatitis is defined as the manifestation of cholestasis derived from chronic hepatitis and posthepatic cirrhosis, with the most common cause being HBV and HEV super-infection. Long-term severe jaundice contributes to secondary biliary cirrhosis and even hepatic failure due to exacerbated liver injury.

In addition to conventional drugs used for liver protection, UDCA, SAME, tolynicate and naphthylacetic acid, and some traditional Chinese medicine preparations for activating blood circulation and eliminating stasis are also considered.^{6,15}

Zhang et al showed that the liver function recovery rate was significantly higher in the UDCA group compared with the control group after four weeks of treatment. Some reports suggest adrenocortical hormone can be administered for a short period under contraindication ruling out conditions.² One hundred and fifty cases of chronic cholestatic hepatitis were randomly divided into four groups: SAME group, glucocorticoid group, prostaglandin E1 group, and artificial liver group in a study by Wang et al. The results showed that jaundice was significantly reduced, liver function and clinical symptoms were rapidly recovered, and the course of disease was short in the SAME group, with similar effects observed in the prostaglandin E1 group. Although a good therapeutic effect was also observed in the artificial liver group, this treatment is associated with greater costs. Cautious use of glucocorticoids is indicated by the prolonged course of disease and risk of complications, such as bacterial or fungus infection, and bleeding observed in the glucocorticoid group. Wang et al demonstrated that SAME can be used in acute or chronic cholestatic hepatitis due to greater tolerance and jaundice reduction compared with conventional drugs.^{48,49}

Recommendations

All types of viral hepatitis can cause cholestatic hepatitis, with HBV and HEV being the most common cause of induced cholestatic hepatitis in adults, and CMV being the most common cause in infants.

Therapeutic agents include UDCA, SAME, and a combination of Traditional Chinese and Western medicine (II).

Adrenocortical hormones can be used for a short period with close monitoring under the condition of contraindication ruling out (III).

Alcoholic liver disease with cholestasis

Alcoholic liver disease is caused by excessive alcohol consumption, with the clinical manifestations of fatty liver in the initial stages, followed by alcoholic hepatitis, liver fibrosis and cirrhosis.

Cholestasis occurs in various alcoholic liver diseases. However, acute alcoholic cholestasis is rare and cholestasis is also rarely developed in alcoholic fatty liver. Approximately 25% of chronic alcoholic liver disease is accompanied by intrahepatic cholestasis and always indicates a poor prognosis.⁵⁰

The diagnosis of this disease requires a long history of drinking, without specific manifestations, such as right epigastric pain, anorexia, acratia, weight-loss or jaundice. It can be diagnosed through observation of biochemical indexes, such as elevated AST, ALT, γ GT, TBil, PT, MCV and AST/ALT >2. Viral hepatitis, drug and toxic liver damage should be ruled out.

Abstinence is the major therapeutic measure for alcoholic liver disease. The patient's state of nutrition should also be considered. Conventional medical treatments include polyene phosphatidyl choline, glycyrrhizic acid preparations and silibinin.⁵⁰ A randomized, double-blind trial was performed in 123 patients (classified into Child-Pugh class A and class B) treated with SAME or placebo for two years.⁵¹ The results showed that the overall rate of mortality/liver transplantation at the end of the trial were significantly higher in the placebo group compared with the SAME group (29% vs. 12%, $P = 0.025$), and differences in the 2-year survival curves (defined as the time to death or liver transplantation) between the two groups were also statistically significant ($P = 0.046$). These results indicate that long-term treatment with SAME improves survival or delays the requirement for liver transplantation in patients with alcoholic liver cirrhosis, especially in those with less advanced liver disease. Some other investigators have reported that combining SAME and naltrexone improves the TBil recovery rate and decreases the incidence of alcohol withdrawal syndrome. Tolynicate and naphthylacetic acid have also been demonstrated to be effective in improving pruritus on the basis of abstinence.⁵²

In cases of severe cholestasis, adrenocortical hormone is recommended when the Maddrey score exceeds 32 and hormone contraindications are ruled out, such as gastrointestinal bleeding and bacterial infection.⁵³ Administration of the hormone should be terminated to prevent adverse reactions if the jaundice did not disappear and no response is indicated after seven days of treatment.

Recommendations

Chronic alcoholic liver disease with cholestasis usually indicates a poor prognosis (II).

Abstinence is the major therapeutic measure for alcoholic liver disease although the patient's state of nutrition should also be considered (III).

SAME may improve the biochemical indicators, survival or delay the requirement for liver transplantation in patients with alcoholic liver cirrhosis (II).

In cases of severe cholestasis, treatment with adrenocortical hormone is recommended for one or two weeks if the Maddrey score exceeds 32 and hormone contraindications such as gastrointestinal bleeding and bacterial infection are ruled out (II).

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