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CONSENSUS

Expert Consensus on the Diagnosis and Treatment of Cholestatic Liver Disease

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

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Abstract

This document presents the latest research findings on the diagnosis and treatment of Chronic Liver Disease (CLD) using evidence-based principles. Widely regarded by experts as a definitive reference, this work acknowledges the multifaceted nature of CLD, influenced by numerous factors. To optimize therapeutic outcomes, a combination of standardized and personalized treatments is recommended. Additionally, an expert committee will regularly update the content to integrate accumulating clinical evidence, promoting consensus in CLD diagnosis and treatment.

Introduction

Cholestatic liver disease (CLD) poses a significant clinical challenge, primarily characterized by cholestasis. Over recent years, there has been a remarkable surge in knowledge pertaining to the diagnosis and treatment of CLD. To consolidate this wealth of information, a collaborative effort was undertaken by leading experts in China, facilitated by the editorial offices of the Chinese Journal of Experimental and Clinical Infectious Diseases (Electronic Edition) and Chinese Journal of Liver Diseases (Electronic Edition). This endeavor has culminated in the development of the Chinese Expert Consensus for the Diagnosis and Treatment of CLDs, hereafter referred to as the consensus.

This comprehensive document outlines the latest research findings on the diagnosis and treatment of CLD, grounded in the principles of evidence-based medicine. The strength of evidence is categorized and presented in Table 1 (Heathcote, 2007), providing a clear reference for healthcare professionals. With the recognition that CLD is influenced by a multitude of factors, experts unanimously advocate for a combined approach utilizing both standardized and personalized treatments, aimed

Table 1. Level of evidence criteria

Level of Evidences	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

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at achieving optimal therapeutic outcomes.

To ensure ongoing relevance and applicability, an expert committee has been established to continuously update the content. This iterative process will incorporate emerging clinical evidence, fostering consensus in the diagnosis and treatment of CLD. By integrating accumulating knowledge and insights from diverse sources, this expert consensus seeks to serve as an authoritative guide for healthcare practitioners, empowering them to deliver the highest standard of care to patients with cholestatic liver disease.

Definition, Classification, and Diagnostic Approaches for Chronic Liver Disease (CLD)

1. Definition

Chronic Liver Disease (CLD) is a prevalent liver disorder characterized by impaired bile formation and secretion, as well as abnormal biliary excretion (Heathcote, 2007). Depending on the underlying cause, CLD can be classified as hepatocellular cholestasis. Symptoms persisting for more than six months are diagnosed as chronic cholestasis, bile ductular cholestasis, or mixed cholestasis. Biochemically, CLD is diagnosed if alkaline phosphatase (AKP) levels exceed 1.5 times the upper limit of the normal range (ULN), and γ-transpeptidase (γGT) levels exceed 3 times ULN.

2. Common Etiological Classification of Adult CLD (Table 2) (EASL Clinical Practice Guidelines, 2009)

3. Diagnostic Approach (Heathcote, 2000; Invernizzi et al., 2007)

The diagnosis of suspected cholestasis follows the steps outlined below (refer to Figure 1):

3.1 History Inquiry

Thorough inquiry should encompass previous history, family history, medical history, and alcohol intake.

3.2 Physical Examination

1) Abdominal Ultrasound Examination and Computed Tomography (CT) Scan

These imaging techniques are employed to exclude extrahepatic bile duct obstruction. Endoscopic ultrasonography (EUS) may be performed if distal obstruction of the biliary tract is suspected.

2) Magnetic Resonance Cholangiopancreatography (MRCP)

MRCP is recommended for CLD patients with unexplained causes. Endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for highly selective cases. If treatment is not anticipated, MRCP or EUS should be prioritized over ERCP due to the relatively higher risk of complications and mortality

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 angeitides), 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's 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)	

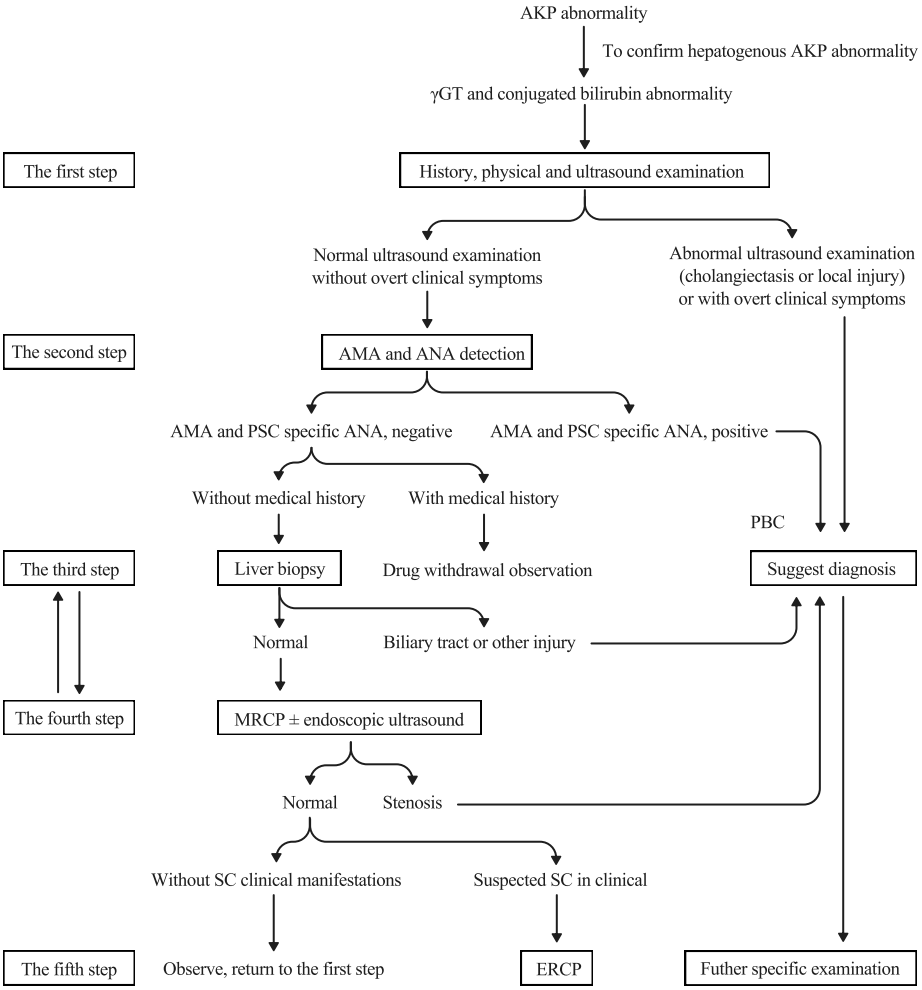

Figure 1. Diagnosis procedure for adult CLD

associated with ERCP.

3.3 Laboratory Examinations

Laboratory evaluations should include liver function tests, viral serological diagnostics, and autoantibody screening. Liver biopsy is warranted for cases of unexplained intrahepatic cholestasis or in patients negative for antimitochondrial antibodies (AMA).

3.4 Recommendations

Thorough history inquiry and physical examination are essential (III). Ultrasound and CT scans are the initial non-invasive imaging modalities for identifying intrahepatic and extrahepatic cholestasis (III). Serum AMA testing is crucial for diagnosing chronic intrahepatic cholestasis (III). MRCP, EUS, ERCP, and liver biopsy should be considered for further evaluation (II).

Treatment Strategies for Chronic Liver Disease (CLD)

1. Etiological Treatment

CLD with different etiologies necessitates tailored treatment strategies.

2. Symptomatic Treatment

2.1 Ursodeoxycholic Acid (UDCA)

UDCA administration is an effective treatment for the majority of CLD patients. By stimulating endogenous bile acid (BA) excretion, UDCA modifies the composition of BAs, increasing the proportion of hydrophilic BAs. These effects protect hepatocytes and cholangiocytes from the toxic effects of endogenous BAs, prevent mitochondrial membrane damage induced by hydrophobic BAs, inhibit liver cell apoptosis, improve serum function and liver histological features, slow the progression into hepatic fibrosis, cirrhosis, and esophageal varices, and ultimately prolong the survival time of CLD patients.

2.2 Glucocorticoids and Other Immunosuppressors

Glucocorticoids reduce T lymphocyte activation by suppressing the production of proinflammatory cytokines and the expression of cell adhesion molecules. They selectively inhibit antibody production by B lymphocytes. Azathioprine, when metabolized into mercaptopurine, acts as a purine antagonist,

interfering with DNA synthesis and lymphocyte proliferation. Combination therapy with reduced doses of glucocorticoids and azathioprine can enhance therapeutic effects and reduce adverse reactions in some CLD patients.

2.3 S-Adenosyl-L-methionine (SAMe)

SAMe is a naturally occurring substance synthesized in human tissues. Through transmethylation, SAMe increases membrane phospholipid content, membrane fluidity, and Na+-K+ ATP enzyme activity, thereby accelerating BA transport in the liver. SAMe also boosts glutathione and cysteine production in liver cells, enhancing detoxification and protection against free radical damage. Additionally, SAMe aids in the prevention of intrahepatic cholestasis by facilitating the combination of taurine and BA to increase its solubility.

3. ERCP and Endoscope-Assisted Treatment

Diagnostic ERCP is considered a standard option for suspected Primary Sclerosing Cholangitis (PSC). Complications are rare when limited to diagnostic ERCP. However, the rate of complications increases to over 14% when endoscope-assisted interventions such as sacculus expansion, endoscopic papillotomy, or stent implantation are performed (Bangarulingam et al., 2009).

4. Liver Transplantation

Liver transplantation significantly improves the survival of patients with advanced CLD (Milkiewicz, 2008; Gautam et al., 2006). Indications for transplantation in CLD align with those for hepatic failure from other causes. Liver transplantation may be recommended for decompensated cirrhotic patients with intolerable quality of life or life expectancies less than one year due to refractory ascites, spontaneous bacterial peritonitis, recurrent variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma.

5. Blood Purification

CLD often involves the presence of autoantibodies, immune complexes, and substance deposition. Blood purification techniques, including plasma exchange (PE), plasma separation and adsorption (PSA), and molecular adsorbent recycling systems (MARS), can eliminate pathogenic and harmful substances, potentially improving patient condition and providing symptom relief. These techniques are particularly useful in cases of severe jaundice or pruritus.

6. Traditional Chinese Medicine and Other Treatments

Cholestatic hepatitis, a subset of CLD, is classified as a jaundice disease in Traditional Chinese Medicine. Treatment methods based on syndrome differentiation include clearing heat and promoting diuresis, activating blood and dissolving stasis, and cooling the blood and reducing phlegm. GALLE-DONAU, a compound preparation of alpha-naphthylacetic acid and methyl benzyl alcohol nicotinate, stimulates physiologic choleresis and exhibits significant anti-inflammatory effects. It alleviates inflammatory edema in the portal area and bile capillaries, improving intrahepatic cholestasis.

Common Treatments for Chronic Liver Disease (CLD)

1. Primary Biliary Cholangitis (PBC)

PBC is characterized by major symptoms such as fatigue, pruritus, and jaundice. The key diagnostic marker for PBC is the presence of antimitochondrial antibodies (AMA), with a positive rate exceeding 90% and a specificity of over 95%. AMA is detected through indirect immunofluorescence, with a titer ≥ 1:40 considered a positive reaction. In most Chinese liver disease research centers, the lowest dilution for detecting positive reactions is 1:100, although further studies are needed to assess potential false negatives at this dilution. The detection of the anti-PDC-E2 subtype (anti-PDC-E2 antibodies) is recommended as an additional effective measurement indicator. Non-specific AMA is detected in at least 30% of PBC patients (Heathcote, 2000).

In adult patients, a diagnosis of PBC can be made when unexplained increased AFP levels are accompanied by AMA (≥ 1:100) and anti-PDC-E2 antibodies. Liver biopsy is not essential for these patients but can be used to assess disease activity and staging (III). However, if specific antibodies are absent, liver biopsy is essential for diagnosing PBC. Additionally, liver biopsy is helpful in differentiating from other diseases when inappropriate serum transaminase and IgG levels increase (III). Patients with positive AMA but normal liver serology should be followed up annually and regularly examined for CLD-related biochemical markers (III).

1.1 Treatment for PBC

1）Ursodeoxycholic Acid (UDCA)

Long-term studies have shown that UDCA administration at a dose of 13-15 mg/kg/day is justified for treating PBC patients, as it significantly improves their long-term survival (see Table 3) (Corpechot et al., 2005; Ter Borg et al., 2006; Pares et al., 2006; Corpechot et al., 2008).

2）Corticosteroids and Other Immunosuppressors

Prednisolone improves serological and histologic liver indices but may lead to significant decreases in bone mineral density, limiting its long-term use in PBC patients (EASL Clinical Practice Guidelines, 2009). Azathioprine and cyclosporine are not recommended as standard PBC treatments (EASL Clinical Practice Guidelines, 2009).

3）Liver Transplantation

Liver transplantation significantly improves the survival of advanced PBC patients (Milkiewicz, 2008; Gautam et al., 2006). Indications for transplantation are similar to those for hepatic

failure due to other causes. Transplantation may be considered when decompensated cirrhotic patients have an intolerable quality of life or a life expectancy of less than one year due to refractory ascites, spontaneous bacterial peritonitis, repeated variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma. Transplantation should also be considered for PBC patients presenting with serum bilirubin content exceeding 6 mg/dL (103 μmol/L), Model for End-stage Liver Disease (MELD) score > 12 (Malinchoc, 2000), intolerable pruritus, or frequent fractures caused by osteoporosis.

1.2 Recommendations

UDCA should be administered at a dosage of 13-15 mg/kg/day (I) for PBC patients, including chronic asymptomatic patients (II). The long-term effects of UDCA can be observed in early-stage patients or those with good biochemical responses (II), which should be evaluated after one year of treatment. Consensus is lacking on how to treat patients with poor biochemical responses (III). Liver transplantation can be considered for advanced patients 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 of less than one year due to refractory ascites, spontaneous bacterial peritonitis, repeated variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma (II).

2. PBC-AIH Overlap Syndrome

2.1 Diagnosis of PBC-AIH Overlap Syndrome

PBC-AIH Overlap Syndrome is a commonly observed liver disease condition. Diagnostic criteria for PBC-AIH Overlap Syndrome are outlined in Table 4 (EASL Clinical Practice Guidelines, 2009).

2.2 Treatment of PBC-AIH Overlap Syndrome

Treatment recommendations for PBC-AIH Overlap Syndrome are derived from retrospective or non-randomized studies. Simultaneous administration of UDCA and immunosuppressors in PBC-AIH Overlap Syndrome patients remains controversial (Qiu et al., 2008). A retrospective cohort study demonstrated that the biochemical response and survival rate after 24 weeks of UDCA treatment in 12 cases of PBC-AIH Overlap Syndrome

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

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

Notes: Standard for "Good biochemical response" to UDCA

[a]: "Barcelona" standard [18]: AKP content decreased by 40% or return to normal after one year treatment

[b]: "Paris" standard [19]: Serum bilirubin content ≤ 1 mg/dl (17 μmol/L), AKP ≤ 3 times ULN and AST ≤ 2 times ULN after one year of treatment

Table 4. Diagnostic criteria for PBC-AIH Overlap Syndrome

PBC criterion	AIH criterion
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 clastic 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.

were similar to those observed in 159 cases of PBC without AIH (Josh et al., 2002).

Additionally, Chazouillères et al. (2006) reported that 17 cases of PBC-AIH Overlap Syndrome were divided into two groups: one receiving UDCA + immunosuppressors and the other receiving UDCA treatment alone (follow-up: 7.5 years). The results showed that four out of six patients in the UDCA + immunosuppressors group achieved biochemical responses in terms of AIH features (ALT < 2 × ULN and IgG < 16 g/L), and fibrosis did not progress. In contrast, the UDCA treatment alone group showed biochemical responses in only three out of eleven patients, with increased fibrosis observed in four patients. These findings suggest that a combination of glucocorticoids and UDCA may be the optimal therapeutic regimen for most diagnosed PBC-AIH Overlap Syndrome patients. An alternative approach involves treating patients initially with UDCA alone and then introducing glucocorticoids if an ideal biochemical response is not achieved after three months (Chazouillères et al., 2006). The initial prednisone dosage is 0.5 mg/kg/day, which is gradually reduced upon detecting decreased levels of glutamic-pyruvic transaminase. The treatment duration is more than six months.

Other immunosuppressors, such as azathioprine, have shown promise as alternatives to glucocorticoids for treating AIH patients, but no data currently exist regarding their use in PBC-AIH Overlap Syndrome patients. Cyclosporine A has demonstrated therapeutic effects in corticosteroid-resistant patients (Rust et al., 2008). Immunosuppressors are typically necessary when AIH occurs concurrently with UDCA treatment (i.e., sequential overlap) (Poupon et al., 2006).

2.3 Recommendations

A gold standard for diagnosing PBC-AIH Overlap Syndrome is currently lacking, and only some criteria can be considered as reference (II). PBC-AIH Overlap Syndrome should not be overlooked once a patient is diagnosed with PBC, as it has important implications for treatment strategies (II). A combination of glucocorticoids and UDCA is the recommended treatment regimen for PBC-AIH Overlap Syndrome patients (II). An alternative option is to initially treat patients with UDCA alone and introduce glucocorticoids if an ideal biochemical response is not achieved after a specified period (e.g., three months) (II). For patients requiring long-term therapy, lower steroid dosages should be considered (III).

3. Primary Sclerosing Cholangitis (PSC)

3.1 Diagnosis of PSC

PSC is a chronic form of CLD characterized by inflammation and fibrosis in both the intrahepatic and extrahepatic bile ducts. The disease causes irregular damage to the biliary tract, including multiple stenosis, and progresses towards cirrhosis and liver failure.

While the exact etiology of PSC remains unknown, there is evidence of genetic predisposition. The disease primarily affects males, with a male-to-female ratio of 2:1. PSC can occur in both children and the elderly, but the average age of onset is around 40 years. More than 80% of PSC patients also suffer from inflammatory bowel disease (IBD), predominantly ulcerative colitis (UC). Therefore, a typical PSC patient is a young or middle-aged man presenting with biochemical and clinical features of both CLD and IBD.

A definitive diagnosis of PSC requires the fulfillment of the following criteria: elevated serological markers of cholestasis (such as AKP and γGT) that cannot be attributed to other causes, as well as characteristic bile duct changes observed through magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), including multiple stenosis and segmental dilatation (Maggs et al., 2008). Some patients who exhibit clinical, biochemical, and histologic features of PSC but have normal cholecystography are classified as having "ductular PSC" (particularly when associated with IBD) or "Proteus syndrome." It is crucial to exclude secondary or other cholestatic diseases in the diagnostic process.

3.2 Treatment of PSC

1) Ursodeoxycholic Acid (UDCA)

UDCA, known for its efficacy in treating PBC, is considered a potential therapeutic option for PSC (Olsson et al., 2005). In the early 1990s, a study demonstrated improvements in biochemical and histological parameters in partial PSC cases following administration of UDCA at a dosage of 10-15 mg/kg/day. Subsequently, a randomized, double-blind study conducted by Lindor et al. in 1997 included 105 patients with well-documented PSC, comparing UDCA (13-15 mg/kg) with placebo. The results revealed that UDCA, but not placebo, was associated with improvements in serum alkaline phosphatase, aspartate aminotransferase, bilirubin, and albumin levels after two years of follow-up. However, UDCA did not lead to significant changes in liver histology or symptom grading. Additionally, a Scandinavian study enrolled 219 randomized patients who received 17-23 mg/kg/day of UDCA or placebo for 5 years (Olsson et al., 2005). The findings demonstrated a significantly improved survival rate in the UDCA group compared to the placebo group. However, no significant difference was observed compared to previously administered UDCA at a lower dose, and biochemical responses were relatively poor compared to other studies, suggesting variations in compliance among different populations. More recently, a multicenter study involving 150 patients failed to show clear benefits of UDCA at a higher dose of 28-30 mg/kg/day in terms of the primary endpoint, including liver transplantation and phlebeurysm, despite improvements in biochemical characteristics (Mitchell et al., 2001; Cullen et al.,

2008; Lindor et al., 2008). Consequently, the role of UDCA in slowing the progression of PSC-related liver diseases remains uncertain, and a higher dose may be potentially harmful in advanced disease stages.

2) Immunosuppressors and Other Preparations

Currently, there is no evidence supporting the significant involvement of glucocorticoids and other immunosuppressors in the activity or outcomes of PSC. Several immunosuppressors, including prednisone, budesonide, azathioprine, cyclosporine A, methotrexate, tacrolimus, pentoxifylline, colchicine, and penicillamine, have been investigated in randomized, placebo-controlled studies, but none have demonstrated sufficient efficacy to warrant their recommendation for the treatment of PSC.

3) Endoscopic Retrograde Cholangiopancreatography (ERCP) and Endoscope-Assisted Therapy

ERCP has been established as a standard diagnostic procedure for suspected PSC (Bangarulingam et al., 2009). However, the introduction of endoscope-assisted interventions during ERCP, such as sacculus expansion, endoscopic papillotomy, and stent implantation, has been associated with an increased rate of complications, exceeding 14%.

Both animal and human studies have demonstrated that endoscope-assisted therapy for biliary strictures can improve liver biochemical markers, alleviate pruritus symptoms, and reduce the risk of cholecystitis recurrence. Therefore, symptomatic patients may undergo repeated endoscope-assisted dilatation therapy in the main bile duct.

4) Liver Transplantation

Liver transplantation remains the definitive treatment option for end-stage PSC patients, offering the potential for a complete cure. In experienced transplant centers, the one-year and ten-year survival rates after liver transplantation are approximately 90% and 80%, respectively.

5) Recommendations

Extensive data has shown that UDCA at a dosage of 15-20 mg/day can improve serological and alternative prognostic indexes (I), but its impact on overall survival remains inconclusive (II). Consequently, UDCA is not universally recommended as a standard therapeutic drug for PSC based on the current limited evidence. Glucocorticoids and other immunosuppressors are not recommended for the treatment of adult PSC, unless there is evidence of overlap syndrome (II). Bile duct dilatation therapy is indicated when significant biliary strictures are accompanied by evident cholestasis (II). Liver transplantation should be considered for end-stage PSC patients (II), as well as patients with atypical cholangiocyte hyperplasia or severe recurrent bacterial cholangitis (II).

4. Intrahepatic Cholestasis of Pregnancy (ICP)

ICP, also known as obstetric cholestasis (OC), is a pregnancy-specific disorder that typically occurs in the latter half of pregnancy and is characterized by pruritus, elevated serum aminotransferases, and bile acid levels, which resolve after delivery (Lammert et al., 2000). The exact cause of ICP is complex and not fully understood. Incidence rates of ICP vary geographically, ranging from 6.5% to 15.6% in high-risk areas such as Chile and South Africa, 1% to 4% in Asian high-risk areas like the Yangtze river basins in China, and 0.4% to 2.0% in Europe (Northern Europe high-risk areas: Gulf of Bothnia, Baltic Sea), with rates of 0.2% to 0.8% in Australia. While ICP resolves after childbirth with a favorable prognosis for the pregnant woman, it can lead to fetal distress, premature birth, and perinatal death. However, advances in pregnancy and newborn care have significantly reduced perinatal mortality, bringing it close to that of the general population (Brites, 2002).

4.1 Diagnosis

ICP can be diagnosed in pregnant women experiencing pruritus as the main symptom, after excluding other skin and liver diseases. Liver function tests are crucial in such cases. ICP diagnosis should be considered in cases of pruritus with unknown causes, accompanied by mild to moderate increases in aminotransferases and bile acid levels (> 10 μmol/L) (Hay, 2008). Additionally, ICP may present with mild jaundice and liposoluble dyspepsia. Pregnancy alone can be the cause of pruritus and abnormal biochemical markers. Symptoms, signs, and abnormal biochemical markers rapidly disappear or return to normal after delivery. Liver function and bile acid levels should be reevaluated ten days postpartum. If abnormal liver function persists at six months postpartum, other chronic liver diseases such as PBC, PSC, and chronic hepatitis should be prioritized, as they are characterized by pruritus in the latter half of pregnancy.

The diagnosis of ICP requires the exclusion of other skin and hepatobiliary conditions and follow-up visits postpartum. Diseases to be ruled out include autoimmune chronic active liver disease, liver damage due to hepatitis viruses, Epstein-Barr virus, cytomegalovirus, and ABCB4 deficiency (Trauner et al., 2007). Ultrasonography can help exclude other severe liver diseases and hepatolithiasis. The patient's condition should be evaluated every one to two weeks. ICP is not associated with significant deviations in alanine aminotransferase (ALT) and serum bilirubin levels < 170 μmol/L (10 mg/dL), nor with normal coagulation function. There is no clear relationship between the severity of ICP symptoms and abnormal biochemical markers or fetal death. Thus, abnormal biochemical markers should not be the sole factor in deciding to terminate the pregnancy. However, clinical studies have indicated that the duration of pruritus and serum bile acid levels are related to fetal outcomes. Bile acid levels > 40 μmol/L and alanine aminotransferase (ALT) > 200 U/L indicate adverse fetal outcomes (Hay, 2008).

Perinatal risk factors can be assessed using the following algorithm: bile acid concentration × duration of exposure/gestational age.

4.2 Pharmacotherapy

1) UDCA

UDCA is classified as a category B drug for pregnancy by the US FDA and can be used for the treatment of ICP during the second or third trimester (Williamson et al., 2004). It has shown efficacy and safety for both the mother and fetus (Glantz et al., 2005). A dosage of 10-20 mg/kg/day of UDCA has been established as the first-line treatment for ICP based on an 8-week randomized controlled study (Kondrackiene et al., 2005). Pruritus and liver function improved in 67% to 80% of ICP patients. However, it remains unclear whether UDCA reduces antenatal complications, as a recent study showed decreased complication rates in both the placebo and UDCA groups. Although UDCA is not approved for use during breastfeeding, the active component of UDCA is not detected in breast milk. UDCA should not be administered during the first three months of pregnancy.

2) SAMe

If pruritus does not significantly improve after several days of UDCA administration, a higher dose of UDCA (25 mg/kg/day) or SAMe can be considered (Binder et al., 2006; Roncaglia et al., 2004). SAMe has been approved for the treatment of ICP by the SFDA.

3) Corticosteroids

The use of low-dose prednisone during pregnancy and lactation is considered safe, although administration during the first three months of pregnancy increases the risk of cleft lip in the fetus. There have been reports of increased risk of premature rupture of membranes and hypoadrenia in organ transplant cases. Hexadecadrol (12 mg/day) has a therapeutic effect on ICP when administered for seven days at a dose of 12 mg/day, followed by gradual dose reduction and withdrawal after ten days. However, due to potential harm to the fetus and neonate, hexadecadrol is not recommended as the optimal treatment for ICP. Glucocorticoids are essential 35 weeks before pregnancy to promote fetal lung development.

4) Azathioprine

Although some animal studies have shown teratogenic effects, it is generally believed that azathioprine is safe for use during pregnancy. Treatment experiences have accumulated from the widespread use of azathioprine in female AIH patients, rheumatoid arthritis, IBD, and organ transplantation. However, the benefits and risks should be thoroughly evaluated before initiating treatment. Azathioprine is present in breast milk, although at low levels (Benjaminov et al., 2004).

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

Fetal monitoring advances and the option of pregnancy termination have significantly contributed to the reduction of perinatal mortality. At week 35, termination of pregnancy should be considered in cases of uncontrolled progressive disease and contractions, abnormal fetal movements, absent fetal heart rate variability, negative stress test response, and meconium-stained amniotic fluid. Fetal hypoxia is not detected when the disease remains stable and fetal monitoring is intensified.

5) Safety Assessment of Drugs for Chronic Liver Disease (CLD) in Pregnancy

Disease progression is generally halted when patients present with mild or stable CLD during pregnancy and childbirth. However, changes may occur in patients with AIH or overlap syndrome. Therefore, prednisone ± azathioprine should be continued during pregnancy in AIH patients to prevent recurrent disease, which may pose a greater risk than the associated risks of these medications. Table 5 summarizes the safety assessment of drugs used in CLD during pregnancy (Mahadevan et al., 2006).

4.3 Recommendations

1) Defining characteristics of ICP

A) Pruritus during pregnancy

B) Elevated serum ALT and bile acid levels

C) Exclusion of other diseases causing abnormal liver function and pruritus (II). Recovery of liver function postpartum can aid in ICP diagnosis.

2) Incidence of premature birth

ICP patients (idiopathic or iatrogenic) have an increased risk of premature birth (II). There is a need for more detailed recommendations for fetal monitoring (III). While UDCA can alleviate pruritus symptoms and improve liver function (I), there is insufficient evidence to support its use in reducing fetal

Table 5. Safety assessment of drugs for CLD

Drug	Harm to fetus (FDA grade)	Security of use
UDCA	B	Low risk
Prednisolone	C	Low risk: increased risk of cleft lip and hypoadrenia
Azathioprine	D	Low risk

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

complications (II).

3) For patients in the second or third trimester of pregnancy

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

4) For AIH patients during pregnancy

Administration of prednisone ± azathioprine should be continued for AIH patients during pregnancy to prevent recurrent disease, which may pose a greater risk than the associated risks of these drugs (III).

5. Drug-induced CLD

Drug-induced liver damage can manifest as hepatocellular cholestasis, hepatocellular damage, or a mixed type. Cholestasis-type drug-induced CLD accounts for approximately 20% to 25% of cases, characterized by elevated alkaline phosphatase (AKP) > 2 × ULN or an R value (ALT/ULN and AKP/ULN ratio) ≤ 2 (Wu et al., 2008).

Various drugs can cause different types of liver damage (Ramachandran et al., 2009). Common drugs known to induce CLD include angiotensin-converting enzyme inhibitors, amoxicillin/clavulanic acid, wintermin, chlorpromazine, erythrocin, and Chinese herbal medicines.

The onset of drug-induced CLD is usually insidious, occurring after one month or more of drug administration. Clinical manifestations may include jaundice, rash, anorexia, fatigue, discomfort, epigastric pain, pruritus, right upper abdominal tenderness, and hepatomegaly. Pruritus is a specific symptom of CLD, present in 20% to 50% of jaundiced patients.

Laboratory examination reveals elevated AKP, γGT, and other bile duct injury markers such as bile acids and aminotransferases, with negative viral markers and AMA.

The key to treatment is discontinuation of the drug responsible for liver damage and avoidance of alternative medications from the same biochemical family, as they may pose a risk of cross-toxicity due to similar chemical structures. Additionally, rapid elimination of the drug is essential.

Studies have shown that treatment with SAMe significantly improves the biochemical indices in patients with drug-induced liver damage (Santini et al., 2003). Another study reported that combination therapy with cyclosporin and ademetionine resulted in no cases of liver cytotoxicity, compared to hepatotoxicity observed in patients treated with cyclosporin alone (Neri et al., 2002). Corticosteroids may be considered in drug-induced CLD, especially in patients with high immune sensitivity, but close monitoring for adverse effects is necessary. For patients with poor responses to drugs and a prolonged course of disease, the introduction of artificial liver support may be warranted (Chou et al., 2008).

Recommendations

Widespread Implications of Drug-Induced Liver Damage:

The detrimental impact of drugs on the liver should not be underestimated, as they have the potential to induce almost all types of liver damage. Astonishingly, 20% to 25% of cases manifest as cholestasis, characterized by elevated levels of alkaline phosphatase (AKP) (> 2 × ULN) or a reduced R value (≤ 2).

Optimistic Prognosis:Despite the challenges posed by drug-induced liver damage, a glimmer of hope shines through, as the prognosis for affected individuals is relatively good (I).

Unveiling the Treatment Paradigm:The pivotal strategy in combating drug-induced liver damage lies in the decisive actions of withdrawal and elimination, accompanied by a resolute avoidance of alternative medications within the same biochemical family. By adopting this transformative approach, a majority of patients experience a gradual recovery after the withdrawal of the offending drug (III).

Revolutionary Therapeutic Interventions:

Embark on a therapeutic revolution by harnessing the power of innovative interventions. Selecting S-Adenosyl Methionine (SAMe), Ursodeoxycholic acid (UDCA), and potent antioxidants like reduced glutathione can prove to be game-changers in combating drug-induced liver damage (II). In the realm of immune-mediated Chronic Liver Disease (CLD), consider the groundbreaking potential of cortical hormones, pushing the boundaries of treatment possibilities (III).

6. Viral Hepatitis-Induced Chronic Liver Disease (CLD)

All types of viral hepatitis, including both acute and chronic forms, can lead to cholestatic hepatitis. Acute cholestatic hepatitis induced by HBV and HEV is more prevalent and shares similar clinical manifestations with acute icteric hepatitis, such as fever, loss of appetite, nausea, and acholia. As symptoms improve and jaundice progresses, patients may experience pruritus, pale stools, elevated direct bilirubin levels (accounting for 60% of total bilirubin), increased AKP and γGT levels, and positive viral markers.

Chronic cholestatic hepatitis is characterized by cholestasis resulting from chronic hepatitis and posthepatitic cirrhosis, with HBV and HEV super-infection being the most common cause. Prolonged and severe jaundice can contribute to secondary biliary cirrhosis and even hepatic failure due to aggravated liver injury.

In addition to conventional liver protection drugs, therapeutic options such as UDCA, SAMe, tolynicate, naphthylacetic acid, and certain Traditional Chinese medicine preparations that promote blood circulation and resolve stasis are considered (Yang, 2001; Zhang et al., 2005).

Zhang et al. demonstrated that the recovery rate of liver function was significantly higher in the UDCA group compared to the control group after four weeks of treatment ($P < 0.05$). Some reports suggest short-term administration of

adrenocortical hormones, provided contraindications are ruled out. Wang et al. conducted a study with 150 cases of chronic cholestatic hepatitis, randomly dividing them into four groups: SAMe group, glucocorticoid group, prostaglandin E1 group, and artificial liver group. The SAMe group showed a significant reduction in jaundice, rapid recovery of liver function and clinical symptoms, and a shorter disease duration. Similar effects were observed in the prostaglandin E1 group. Although the artificial liver group also exhibited positive therapeutic effects, this treatment is associated with higher costs. Careful use of glucocorticoids is advised due to the prolonged disease course and the risk of complications such as bacterial or fungal infections and bleeding observed in the glucocorticoid group. Wang et al. demonstrated that SAMe can be used in both acute and chronic cholestatic hepatitis due to its better tolerance and efficacy in reducing jaundice compared to conventional drugs (Wang et al., 2001; Wang et al., 2001).

Recommendations

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

Therapeutic agents for viral hepatitis-induced cholestatic hepatitis include UDCA, SAMe, and a combination of Traditional Chinese and Western medicine (II).

Adrenocortical hormones can be used for a short period under close monitoring, provided contraindications are ruled out (III).

7. Alcoholic Liver Disease with Cholestasis

Alcoholic liver disease is a result of excessive alcohol consumption and progresses through stages of fatty liver, alcoholic hepatitis, liver fibrosis, and cirrhosis.

Cholestasis can occur in various types of alcoholic liver diseases. Acute alcoholic cholestasis is rare, and cholestasis is also uncommon in alcoholic fatty liver. Approximately 25% of chronic alcoholic liver disease cases present with intrahepatic cholestasis, which is an indicator of poor prognosis (Fatty Liver and Alcoholic Liver Diseases Study Group of the Chinese Liver Diseases Association, 2006).

Diagnosis of alcoholic liver disease requires a long history of drinking and the absence of specific manifestations such as right epigastric pain, anorexia, acholia, weight loss, or jaundice. Biochemical markers, including elevated AST, ALT, γGT, TBil, PT, MCV, and an AST/ALT ratio > 2, aid in the diagnosis. Other potential causes, such as viral hepatitis, drug-induced liver damage, and toxic liver injury, should be ruled out.

Abstinence from alcohol is the primary therapeutic measure for alcoholic liver disease. The patient's nutritional status should also be considered. Conventional medical treatments include polyene phosphatidylcholine, glycyrrhizic acid preparations, and silibinin for intrahepatic cholestasis (Fatty Liver and Alcoholic Liver Diseases Study Group of the Chinese Liver Diseases Association, 2006).

A randomized, double-blind trial conducted by Mato et al. involved 123 patients classified as Child class A and class B, who were treated with SAMe or placebo for two years. The results demonstrated significantly lower rates of mortality/liver transplantation in the SAMe group compared to the placebo group (29% vs. 12%, $P = 0.025$), with statistically significant differences in the 2-year survival curves (defined as time to death or liver transplantation) between the two groups ($P = 0.046$). These findings suggest that long-term SAMe treatment improves survival and delays the need for liver transplantation in patients with alcoholic liver cirrhosis, particularly those in less advanced stages of the disease. Some investigators have reported that combining SAMe and naltrexone improves TBil recovery rates and reduces the incidence of alcohol withdrawal syndrome. Tolynicate and naphthylacetic acid have also demonstrated effectiveness in relieving pruritus after abstinence (Zhang et al., 2005).

In cases of severe cholestasis, treatment with adrenocortical hormones is recommended when the Maddrey score exceeds 32, and contraindications such as gastrointestinal bleeding and bacterial infection have been ruled out (Barve et al., 2006). Hormone administration should be discontinued if jaundice persists and no response is observed after seven days of treatment.

Recommendations

Chronic alcoholic liver disease with cholestasis is typically associated with a poor prognosis (II).

Abstinence from alcohol is the primary therapeutic measure, with consideration for the patient's nutritional status (III).

SAMe may improve biochemical markers, survival, or delay the need for liver transplantation in patients with alcoholic liver cirrhosis (II).

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

References

[1] Bangarulingam SY, Gossard AA, Petersen BT, Ott BJ, Lindor KD. Complications of endoscopic retrograde cholangiopancreatography in primary sclerosing cholangitis. Am J Gastroenterol. 2009;104(4): 855- 60.

[2] Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(6):318-28.

[3] Brites D. Intrahepatic cholestasis of pregnancy: changes in maternal-fetal bile acid balance and improvement by ursodeoxycholic acid. Ann Hepatol. 2002;1(1):20-8.

[4] Benjaminov FS, Heathcote J. Liver disease in pregnancy. Am J Gastroenterol. 2004;99:2479-88.

[5] Bellmann R, Graziadei IW, Feistritzer C, Schwaighofer H, Stellaard F, Sturm E, Wiedermann CJ, Joannidis M. Treatment of refractory cholestatic pruritus after liver transplantation with albumin dialysis.

Liver Transpl. 2004;10(1):107-14.
[6] Binder T, Salaj P, Zima T, Vítek L. Randomized prospective comparative study of ursodeoxycholic acid and S-adenosyl-Lmethionine in the treatment of intrahepatic cholestasis of pregnancy. J Perinat Med. 2006;34(5):383-91.
[7] Chazouilleres O, Wendum D, Serfaty L, Rosmorduc O, Poupon R. Long-term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. J Hepatol. 2006;44(2):400-6.
[8] Corpechot C, Abenavoli L, Rabahi N, Chrétien Y, Andréani T, Johanet C, Chazouillères O, Poupon R. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48(3):871-7.
[9] Corpechot C, Carrat F, Bahr A, Chrétien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology. 2005;128(2):297-303.
[10] Cullen SN, Rust C, Fleming K, Edwards C, Beuers U, Chapman RW. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective. J Hepatol. 2008;48(5):792- 800.
[11] Barve S, Joshi-Barve S, Song Z, Hill D, Hote P, Deaciuc I, McClain C. Interactions of cytokines, S-adenosylmethionine, and S-adenosylhomocysteine in alcohol-induced liver disease and immune suppression. J Gastroenterol Hepatol. 2006;21 Suppl 3:S38-42.
[12] Chou JW, Yu CJ, Chuang PH, Lai HC, Hsu CH, Cheng KS, Peng CY, Chiang IP. Successful treatment of fosinopril-induced severe cholestatic jaundice with plasma exchange. Ann Pharmacother. 2008;42(12):1887-92.
[13] EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51(2):237-67.
[14] Fatty Liver and Alcoholic Liver Diseases Study Group of the Chinese Liver Diseases Association. Guidelines for diagnosis and treatment of alcoholic liver diseases. Zhonghua Gan Zang Bing Za Zhi (Chin) 2006;14(3):164-6.
[15] Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. Liver Transpl. 2006;12(12):1813-24.
[16] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology. 2004;40(2):467-74.
[17] Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. Hepatology. 2005;42(6):1399-05.
[18] Hay JE. Liver disease in pregnancy. Hepatology. 2008;47:1067-76.
[19] Heathcote EJ. Diagnosis and management of cholestatic liver disease. Clin Gastroenterol Hepatol. 2007;5(7):776-82.
[20] Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology. 2000;31(4):1005-13.
[21] Invernizzi P, Lleo A, Podda M. Interpreting serological tests in diagnosing autoimmune liver diseases. Semin Liver Dis. 2007; 27(2):161-72.
[22] Joshi S, Cauch-Dudek K, Wanless IR, Lindor KD, Jorgensen R, Batts K, Heathcote EJ. Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology. 2002;35(2):409-13.
[23] Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. JAMA. 2003;289(2):17-222.
[24] Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology. 2005;129(3):894-901.
[25] Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009;;50(3):808-14.
[26] Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol. 2000;33(6):1012-21.
[27] Lemoine M, Revaux A, Francoz C, Ducarme G, Brechignac S, Jacquemin E, Uzan M, Ganne-Carrie N. Albumin liver dialysis as pregnancy-saving procedure in cholestatic liver disease and intractable pruritus. World J Gastroenterol. 2008;14(42):6572-4.
[28] Macia M, Aviles J, Navarro J, Morales S, Garcı J. Efficacy of molecular adsorbent recirculating system for the treatment of intractable pruritus in cholestasis. Am J Med. 2003;114(1):62-4.
[29] Maggs JR, Chapman RW. An update on primary sclerosing cholangitis. Curr Opin Gastroenterol. 2008;24(3):377-83.
[30] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864-71.
[31] Mato JM, Cámara J, Fernández de Paz J, Caballería L, Coll S, Caballero A, García-Buey L, Beltrán J, Benita V, Caballería J, Solà R, Moreno-Otero R, Barrao F, Martín-Duce A, Correa JA, Parés A, Barrao E, García-Magaz I, Puerta JL, Moreno J, Boissard G, Ortiz P, Rodés J. S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. J Hepatol. 1999;30(6):1081-9. .
[32] Mahadevan U, Kane S. American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006;131(1):283-311.
[33] Milkiewicz P. Liver transplantation in primary biliary cirrhosis. Clin Liver Dis. 2008;12:461-72.
[34] Mitchell SA, Bansi DS, Hunt N, Von Bergmann K, Fleming KA, Chapman RW. A preliminary trial of high-dose ursodeoxycholicacid in primary sclerosing cholangitis. Gastroenterology. 2001;121(4): 900-7.
[35] Shegani A, Kealey S, Luzi F, Basagni F, Machado JDM, Ekici SD, Ferocino A, Gee AD, Bongarzone S. Radiosynthesis, preclinical, and clinical positron emission tomography studies of carbon-11 labeled endogenous and natural exogenous compounds. Chem Rev. 2023;123(1):105-229.
[36] Olsson R, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, Bell H, Gangsøy-Kristiansen M, Matre J, Rydning A, Wikman O, Danielsson A, Sandberg-Gertzén H, Ung KA, Eriksson A, Lööf L, Prytz H, Marschall HU, Broomé U. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. Gastroenterology. 2005;129(5):1464-72.
[37] Poupon R, Chazouilleres O, Corpechot C, Chrétien Y. Development of autoimmune hepatitis in patients with typical primary biliary

cirrhosis. Hepatology. 2006;44(1):85-90.
[38] Pusl T, Denk GU, Parhofer KG, Beuers U. Plasma separation and anion adsorption transiently relieve intractable pruritus in primary biliary cirrhosis. J Hepatol. 2006;45(6):887-91.
[39] Qiu D, Li X, Wei Y, Ye L, Peng Y, Ma X. Clinical features of 107 autoimmune hepatitis patients and 30 of them with AIH-primary biliary cirrhosis overlap syndrome. Zhonghua Gan Zang Bing Za Zhi (Chin) 2008;16(5):367-71.
[40] Ramachandran R, Kakar S. Histological patterns in drug-induced liver disease. J Clin Pathol. 2009;62(6):481-92.
[41] Roncaglia N, Locatelli A, Arreghini A, Assi F, Cameroni I, Pezzullo JC, Ghidini A. A randomised controlled trial of ursodeoxycholic acid and S-adenosyl-l-methionine in the treatment of gestational cholestasis. BJOG. 2004 ;111(1):17-21.
[42] Rust C, Beuers U. Overlap Syndromes among autoimmune liver diseases. World J Gastroenterol 2008;14(21):3368-73.
[43] Santini D, Vincenzi B, Massacesi C, Picardi A, Gentilucci UV, Esposito V, Liuzzi G, La Cesa A, Rocci L, Marcucci F, Montesarchio V, Groeger AM, Bonsignori M, Tonini G. S-adenosylmethionine (AdoMet) supplementation for treatment of chemotherapy-induced liver injury. Anticancer Res. 2003;23(6D):5173-9.
[44] ter Borg PC, Schalm SW, Hansen BE, van Buuren HR; Dutch PBC Study Group. Prognosis of ursodeoxycholic acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol. 2006;101(9):2044-50.
[45] Trauner M, Fickert P, Wagner M. MDR3 (ABCB4) defects: a paradigm for the genetics of adult cholestatic syndromes. Semin Liver Dis. 2007;27(1):77-98.
[46] Wang BE. Ademetionine 1,4-butanedisulphonate vs traditional Chinese medicine for the treatment of acute viral hepatitis with hepatocellular jaundice. Clin Drug Invest. 2001;21:685-94.
[47] Wang BE. Ademetionine 1,4 butanedisulphonate vs traditional Chinese medicine for the treatment of hepatocellular jaundice complicating chronic viral hepatitis. Clin Drug Invest. 2001;21:765-73.
[48] Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, Swiet M, Johnston DG. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG. 2004;111(7):676-81.
[49] Wu X, You H, Jia J. Clinaical features of drug-induced liver injury: A review of Chinese literatures 2003-2007. Chin Hepatol (Chin). 2008;13:463-66.
[50] Yang X. S-adenosyl-methionine for the treatment of drug-induced liver disease in 20 patients. World Chin J Digestol. 2001;9:807.
[51] Zhang S, Wang J, Han Y. Tolynicate and naphthylacetic acid in treating hepatitis E of elderly patients. Chin J New Drugs Clin Rem. 2005;24:660-2.
[52] Zhang S, Cui L, Liu H, Han Y. Therapeutic effects of Galle-Donau treatment on patients with alcoholic liver disease. Practic Pharm Clini Remi. 2005;8:28-30.