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Review Article

Evaluation and Management of Chronic Cholestatic Liver Diseases

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Abstract

Cholestasis is defined as stagnation or a marked reduction in bile secretion and flow. Cholestatic jaundice can thus be classified as intrahepatic or extrahepatic cholestatic, depending on the level of obstruction to bile flow. It is important to recognize the complications of cholestatic in patients with chronic cholestatic liver disease. The two most common complications of cholestasis are pruritus and fatigue, with the former being the most responsive to treatment. Cholestyramine is the first-line treatment for cholestatic pruritus. Rifampicin and oral opioid antagonist naltrexone are extremely effective second-line treatments. To date, there are no specific treatments for chronic cholestatic fatigue management. Osteoporosis is a complication that can arise in chronic cholestatic conditions. It appears to be more prominent in individuals with cholestatic liver disease than in patients with other chronic liver diseases with an increased risk of fracture. The evaluation of osteoporosis in individuals with chronic cholestasis is similar to that in the general population. Antiresorptive agents such as bisphosphonates are the first-line treatment choice for osteoporosis in patients with chronic cholestasis. Other less common complications include dyslipidemia, fat-soluble vitamin deficiency, and steatorrhea. Understanding and treating these conditions can have a significant impact on the morbidity and quality of life in this group of patients. This review aimed to provide further information about the complications of chronic cholestasis and to highlight evidence-based test practices for the evaluation and effective management of these complications.

Keywords: Chronic cholestatic, Pruritus, Osteoporosis, Dyslipidemia, Fatigue

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Introduction

Cholestasis is defined as a decrease in bile secretion or flow that causes the accumulation of bile in the blood or hepatocytes. Cholestasis can be caused by functional impairment of hepatocyte secretion in bile secretion and/or due to an obstruction at any level of the excretory pathway of bile, from the level of the hepatic parenchymal cells at the basolateral (sinusoidal) membrane of the hepatocyte to the ampulla of Vater in the duodenum. Thus, cholestatic can be classified into two types, intrahepatic and extrahepatic cholestatic, depending on the obstruction of bile flow. Intrahepatic cholestatic or functional cholestatic can be due to a disease involving the liver parenchymal cells and/or the intrahepatic bile ducts, whereas extrahepatic cholestatic or obstructive cholestatic is usually due to excretory block outside of the liver, along with the extrahepatic bile ducts.[1]

There have been only a few reports of chronic cholestatic cases worldwide and in Indonesia. Cholestatic can occur in people of any age, but children and teenagers are more likely to suffer from it since their livers are not yet fully developed. Moreover, there does not seem to be any difference between men and women in terms of how often cholestatic jaundice occurs. Females are at slightly higher risk of biliary atresia and drug-induced cholestatic.[1]

Long-standing cholestasis not only increases morbidity and mortality but also affects the patient's quality of life. This review aimed to provide clinicians with a better understanding of chronic cholestatic complications, which will lead to better evaluation and management in the future.

Chronic Cholestatic

Biliary secretion remains the most important part of liver detoxification and digestion in the intestine. Cholestasis is chronic if it lasts longer than 6 months. Icter, which is another name for jaundice, is the yellowing of the skin, eyes, and mucous membranes. It is caused by high levels of bilirubin in the blood due to severe cholestasis. It is also a sign of the cause, whether pre-, intra-, or post-hepatic.[2] Most cases of chronic cholestasis do not cause any symptoms and occur over a period of several months. In these cases, serum alkaline phosphatase (ALP) levels often increase. High levels of serum gamma-glutamyl transpeptidase (GGT) and/or conjugated bilirubin follow high levels of ALP in the liver. An evaluation of the patient with chronic cholestatic can be looked into in the order below (Figure 1).[2]

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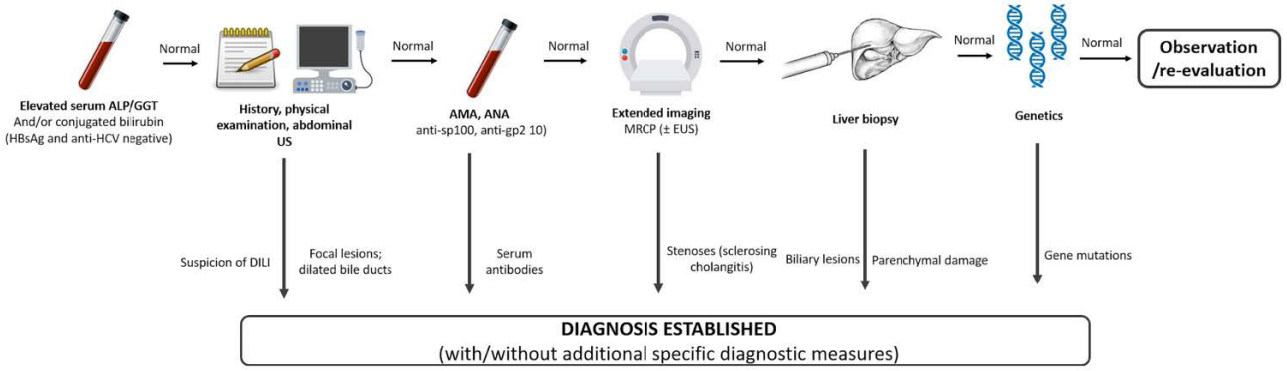

Figure 1. Algorithm for clinical, biochemical, and technical diagnostic measures for chronic cholestatic

History, Physical Examination, Abdominal Ultrasound

Careful history taking, including history of previous medical conditions, and social, travel, and family history, must be performed by clinicians. A few conditions related to chronic cholestasis, such as primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) must be explored. Other conditions, such as repeated trauma related to secondary sclerosing cholangitis, long-standing exposure to chemical substances, and the diesel or gas industry, have been observed in immunoglobulin (Ig) G4-associated cholangitis. Previous medications such as anabolic steroids, herbs, alcohol, and laxative agents must also be considered. Approximately 30% of patients with drug-induced liver injury (DILI) also present cholestasis. DILI occurs mostly within 5-90 days after drug consumption, and suspected drugs must be stopped immediately.[2]

Physical examination included identification of hepatosplenomegaly and extrahepatic signs of advanced liver diseases, such as icter of sclera, skin and mucosa membrane, palmar and plantar erythema, nail abnormality, and scratch lesions, particularly on the arms and legs. While ultrasonography is the first radiological test that should be performed on a patient with chronic cholestasis to rule out biliary ductus obstruction, mass lesions (in and outside of the liver), and gallbladder problems, it is not the only test that should be performed. Normal results will make us suspicious of intrahepatic cholestatic.[2]

Chronic cholestasis can cause several conditions, including complications from underlying diseases, complications related to chronic liver disease due to long-standing cholestasis, and specific conditions related to cholestasis itself. The most common complications of chronic cholestasis are discussed as follows.

Chronic Cholestatic Complications

Diagnosis and Evaluation of Cholestatic Pruritus

Pruritus is one of the most common signs of cholestatic complication. This type of itching is called cholestatic pruritus due to blocked bile secretion. Men are less likely to have it than women. Fluctuations are common and can occur over a long period or in a daily cycle called the circadian rhythm. The fluctuations tend to worsen in the evening. Cholestatic pruritus mainly affects the palms and soles of the feet and hands. There are no primary skin lesions, but the scratch marks can be made worse by eczema, hyperpigmentation, prurigo nodules, and bacterial infections. Pruritus can happen at any stage of liver disease, even in people who do not have jaundice.[3]

Its frequency varies depending on the underlying cause of cholestasis; however, it affects around 25%-80% of individuals with PBC and PSC and 5%-15% of those with chronic hepatitis C. Individuals with chronic hepatitis B or steatohepatitis do not frequently experience itching. The precise mechanism underlying cholestatic pruritus remains unclear. Recent research suggests that lysophosphatidic acid (LPA) may act as a mediator of cholestatic pruritus. Serum enzyme autotoxins convert lysophosphatidylcholine into LPA (ATX). It is a strong neural activator that also regulates neuropathic pain, hair growth, and embryonic implantation. Blood LPA levels are elevated in patients with cholestatic pruritus. Autotaxin (ATX) activity is also related to the severity of cholestatic pruritus. Serum ATX levels are specific for cholestatic-related pruritus, including PBC, PSC, and intrahepatic cholestasis of pregnancy, but not for uremia, Hodgkin's disease, or atopic dermatitis.[4]

Studies have not shown that histamine plays a role in cholestatic pruritus because it is caused by a mechanism different from that of allergic pruritus. There is no difference between people with cholestatic liver disease and normal people in the number of mast cells, the number of nerve cells, or how mast cells and nerve cells work together. Thus, antihistamine drugs are not helpful in alleviating cholestatic pruritus, but they may help people sleep at night if they have mild itching. Erythema and urticaria, which are caused by the release of histamine, are not seen in people with cholestatic pruritus either.[3]

Figure 2 shows how cholestatic pruritus is managed. Anion exchange resins, such as cholestyramine, are the first choice for treating cholestatic pruritus because they work well and are safe. They bind bile salts in the bowel lumen, stopping the flow of bile salts from the intestine to the liver. This causes the hepatocytes to form more bile salts from cholesterol. A placebo-controlled trial showed

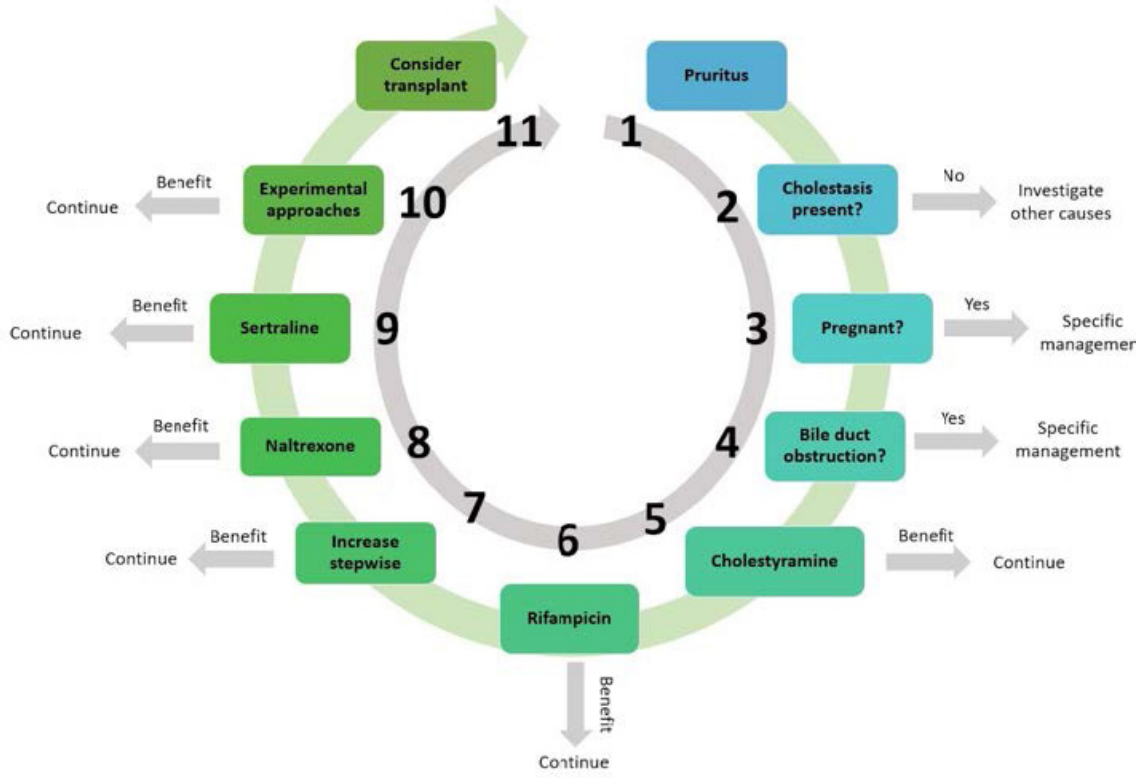

Figure 2. Proposed algorithm for cholestatic pruritus management

that 80%–85% of people who took cholestyramine felt better within 4–11 days, and the relief lasted for up to 32 months. The recommended dose is 4–16 g/d at divided doses. Theoretically, it works best if half the dose is taken 30 minutes before breakfast and the other half is taken 30 minutes after breakfast so that most bile acid is bound as the gallbladder empties. This agent cannot be used to treat everyone because it is difficult for the body to absorb other drugs and can cause stomach problems, such as bad taste, bloating, and constipation. Other bile acid-binding resins like colestipol and colesevelam have not been studied enough to recommend them for this purpose at this time.[5]

The second-line therapy for pruritus is the antibiotic rifampin (RMP), a pregnane X receptor (PXR) agonist, in addition to inducing the P450 system. Recent in vitro studies have shown that RMP inhibits ATX expression in human HepG2 hepatoma cells and hepatoma cells that have too much PXR, but not in hepatoma cells where PXR is turned off. Transcriptional inhibition of ATX expression by PXR may explain, at least in part, why RMP is helpful. Another mechanism by which RMP might stop itching is by activating phase I (P450 system), phase II (1A1), and phase III (export pumps) biotransformation enzymes and pumps, such as the canalicular conjugate export pump (MRP2). This makes it possible for RMP to speed up the removal of bilirubin, bile acids, steroids, and drugs from the body. Even though phenobarbital is also a strong P450 system inducer, it does not reduce pruritus as much as RMP. This suggests that the clinical effect of RMP may not be entirely due to the P450 system induction. RMP has also been shown to be safe and effective for children with cholestatic disease. It works better for children with intrahepatic cholestasis than for those with cholestatic causes outside the liver. Adults should take two or three doses of 300–600 mg/d, and children should take 10 mg/kg/d. A meta-analysis has shown that RMP is a short-term treatment for pruritus that works well and is safe. Approximately 13% of patients experience hepatotoxicity, which can occur as soon as 3 months after treatment has started. Therefore, when taking RMP, serum aminotransferases should be checked regularly. Patients should also be informed that RMP turns the color of urine and tears orange-red. This is a harmless side effect.[3]

Studies have shown that opioids play a major role in pruritus. Opioid antagonists have been studied for the treatment of cholestatic pruritus and may be recommended as third-line agents for treating cholestatic pruritus. They significantly reduced itch and/or scratching behaviors. Nalmefene is an opioid antagonist that can be taken by mouth. It helps in both itching and the amount of bile acid in the blood of patients with cholestatic liver disease. The starting dose is usually 4–10 mg/day, and it slowly increases every two days until the symptoms disappear. The highest dose that has been studied is 240 mgay, but this is not available in most countries, including Indonesia. In another research, pruritus improved significantly in cholestatic patients who were given naloxone (0.4 mg intravenous bolus, then 0.2 μg/kg/min). Another drug, naltrexone (50 mg/d orally), also worked well after 4

weeks. Naloxone should be administered as a selective parenteral agent. It was shown that naltrexone was better than placebo in reducing pruritus and making people feel less tired and less depressed. Opioid antagonists can cause withdrawal symptoms such as loss of appetite, nausea, stomach pain, pallor, cool skin, and high blood pressure. The reaction may start within hours of taking the medicine, but it is temporary and usually moves away within 2–3 days, even if the treatment is continued. Opioid receptor blockers should be administered at very small doses. After itchiness decreases at first, it worsens and stays worse in the first few weeks of treatment. This is known as the breakthrough effect. This effect may be caused by the brain's opiate receptors being turned back on after they were turned down during therapy.[6]

Serotonin antagonists and selective reuptake inhibitors (SSRIs) such as sertraline and paroxetine have been investigated in patients with chronic pruritus. Sertraline, an SSRI, has been associated with a reduction in cholestatic pruritus. Sertraline (75-100 mg/d) treatment resulted in a significant improvement in scratching activity, duration, and itch distribution compared with placebo. However, the mechanism by which serotonin affects itch perception remains unknown. Another feasible option is liver transplantation, although this raises another issue regarding organ transplantation priority.[3]

Diagnosis and Evaluation of Osteoporosis

Osteopenia bone disease is a risk factor for spontaneous fractures and a common cause of chronic cholestasis. According to the National Osteoporosis Foundation, osteoporosis is characterized by reduced bone mass, degradation of bone microarchitecture, and increased fracture risk. Osteodystrophy in cholestasis is the primary cause of osteoporosis in North America. Cirrhosis has been associated to an approximately twofold increase in fracture risk compared to noncirrhotic liver disease.[4] Men, long-term steroid usage, advanced stage of liver disease, and the first year following liver transplantation are all thought to be risk factors for osteoporosis in chronic cholestatic patients.[7]

Osteoporosis can occur in chronic liver illness of any cause, not just cholestasis. The type, severity, and course of underlying liver illness influence the severity of osteoporosis. Osteoporosis appears to be more prominent in individuals with cholestatic liver disease than in patients with other chronic liver diseases with an increased risk of fracture. The prevalence of osteoporosis in patients with PBC ranges from 14.2% to 51.5%. Women with PBC lose bone mass at around twice the rate of age-matched controls. Another significant factor in the development of osteoporosis in women with PBC is menopausal status because estrogen levels strongly influence bone mineral density (BMD). The comparing BMD between the PBC and control subjects before cirrhosis is comparable; however, the incidence of osteoporosis rose in stages III and IV, both PBC and PSC, compared with stages I and II.[3]

One-half of the PBC patients who have a liver transplant have significant bone disease. After liver transplantation, there is a rapid loss of bone over the first 3-6 months, which is thought to be caused by immunosuppressive medicines and catabolic conditions during the peri-transplantation period. During the first four months, bone production rates begin to rise, but they do not keep pace with the rising rate of bone resorption. The frequency of post-transplant fractures is as high as 30%-40% in cholestatic patients, with the highest incidence occurring in the first year after transplantation and progressively decreasing during the following year.[3]

Osteoporosis in cholestatic liver disease is still not well understood, but it is thought to be caused by multiple factors. In cholestatic patients, osteoporosis risk factors include older age, higher Mayo risk score, lower body mass index, menopause, and an advanced histological stage. Higher serum bilirubin levels, which may indicate that PBC is more advanced, are strongly linked to a higher rate of bone loss. In PBC, other factors that appear to directly or indirectly alter bone mass include insulin growth factor-1 deficiency, hypogonadism, and excess alcohol intake. Low vitamin D levels, osteoprotegerin deficiency, collagen type Ia1 gene polymorphisms, and immunosuppressive therapy before and after transplantation.[2,8] BMD measurements at multiple spots can be used to assess the degree and course of bone disease. Dual-energy X-ray absorptiometry measures bone mass precisely. The lumbar spine (L2-L3) and the superior portion of the femur are two common locations. This examination is brief, precise, and minimally invasive.[2]

The World Health Organization (WHO) defines BMD score as a diagnostic criterion for osteoporosis. BMD is expressed as T-score or a z-score. The T-score is the standard deviation number that is above or below the average BMD based on sex and race (not based on age). The T-score categorizes patients into three groups: normal, low bone mass (osteopenia), and osteoporosis. The International Association for Clinical Densitometry recommends combining BMD absolute value and T-score less than -2.5 to diagnose osteoporosis (Table 1).[9]

BMD measurement should be considered in all patients with PBC upon diagnosis and repeated every 2-3 years, according to the American Society for the Study of Liver Diseases. BMD should be measured in all patients with cirrhosis, those using long-term corticosteroids (>3 months), those who have a fragility fracture, and before liver transplantation (Figure 3). The National Institute of Health guidelines suggest prophylaxis with calcium supplementation of 1000 mg/d for all adults and 1500 mg/d for those at risk for osteoporosis, and vitamin D supplementation of 800 IU/day for all adults and 50 000 IU given 2 to 3 times per week for those found to be deficient or at risk forosteoporosis.[2,4,10]

Anti-resorptive and hormone replacement therapies are two types of treatment. Bisphosphonates, which are

Table 1. Osteoporosis criteria based on WHO

Category	Criteria
Normal	BMD within 1.0 SD below the young adult female reference mean (T-score ≥ –1.0)
Osteopenia	BMD between 1.0 and 2.5 SDs below the young adult female reference mean (T-score < –1.0 and > –2.5)
Osteoporosis	BMD ≥ 2.5 SDs below the young adult female reference mean (T-score ≤ –2.5)
Severe Osteoporosis	BMD ≥ 2.5 SDs below the young adult female reference mean and the presence of one or more fragility fractures

Adapted from Handzlik-Orlik et al.[8] The Creative Commons Attribution-NonCommercial 4.0 License, 2016.

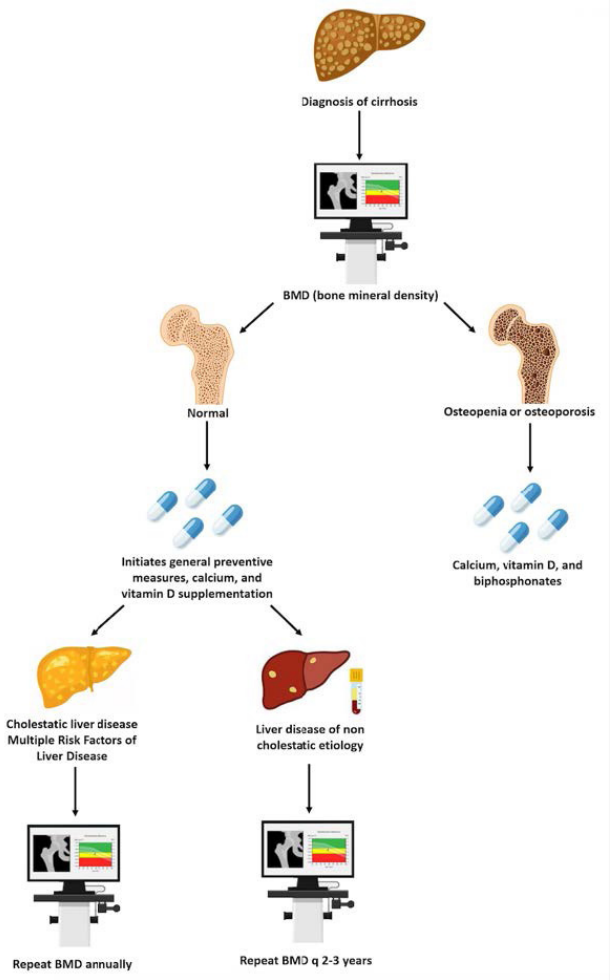

Figure 3. Management algorithm for bone disease in cirrhosis

used to treat postmenopausal osteoporosis, are the major treatment for cholestatic patients with osteoporosis and are typically used in conjunction with calcium and vitamin D.[12] Alendronate 70 mg/wk was found to improve bone mass significantly after 2 years of treatment compared to placebo (Table 2).[11] Alendronate and other bisphosphonate can be started immediately when T-score ≤ -2.5, Z score ≤ -1.5 or if there is another clinical indication.[2,11]

In women with cholestatic liver disease, hormone replacement therapy is regarded as second-line therapy after bisphosphonates for the treatment of osteoporosis. Hormone treatment dramatically slows bone mass loss in postmenopausal women with chronic cholestatic disease. Estrogens were proven to improve BMD after 2 years

Table 2. Treatment options for osteoporosis in chronic cholestasis

Treatment options for osteoporosis in chronic cholestatic	
Calcium	1.500 mg/d
Vitamin D	400-800 IU/d
Hormonal replacement therapy	Varies[a]
Fluoride	50 mg/d
Vitamin K (phytonadione)	1 mg/d
Alendronate	70 mg/wk

Note: [a]Estradiol transdermal 50 µg/d two times a week + medroxyprogesterone 2.5 mg/d.
Adapted from Ahmed et al.[3] Copyright 2014, Springer.

of administration but were associated with a variety of negative effects, such as carcinogenic characteristics and an increased risk of dementia; therefore, estrogen must be taken with caution. Raloxifene, a selective estrogen receptor modulator, has shown potential as an alternative estrogen replacement therapy for postmenopausal osteoporosis. Raloxifene was tested in a pilot study of nine postmenopausal women with PBC, and it resulted in a significant increase in bone mass after one year of treatment.[2]

Vitamin K derivatives, phytonadione, and menaquinone may be useful in the prevention and treatment of cholestatic-related osteoporosis. One study found that patients who received vitamin K had a higher BMD than those who did not. Given the minimal prevalence of adverse effects and established efficacy, vitamin K should be regarded as a potential medication that requires more investigation in the future.[3]

Diagnosis and Evaluation of Hyperlipidemia

Cholestasis is linked to dyslipoproteinemia because the body does not remove cholesterol, phospholipids, and bile salts as it should.[3] About 80% of people with chronic cholestasis have problems with their lipids. High-density lipoprotein (HDL) serum levels are increased in patients in the early stages of PBC. This may be because the levels of hepatic triglyceride lipase decreased. Early in the disease, there are also high levels of serum very low-density lipoprotein and low-density lipoprotein (LDL). However, as the disease worsens, there is a gradual increase in LDL, a drop in HDL, and the appearance of abnormal lipoprotein particles, such as lipoprotein. Surprisingly, these lipid abnormalities are not usually linked to cardiovascular events.[13] In a study done by Allocca and his colleagues showed that there was no increase in the

number of atherosclerotic lesions in the carotid arteries of people with PBC and high cholesterol levels. One reason might be that people with PBC have much higher levels of adiponectin in their blood, which is known to protect the heart, than people with hyperlipidemia without cholestasis. Other research suggests that lipoprotein X (LP-X) protects people with PBC by inhibiting LDL oxidation. This reduces atherogenicity and keeps the integrity of arterial endothelial cells.[3,11]

The LDL serum fraction from patients with chronic cholestasis was found to have three types of lipoproteins; β2-lipoprotein rich in triglyceride or known as lipoprotein-Y (LP-Y), LP-X, and normal LDL. LP-X is rich in equimolar and unesterified cholesterol phospholipids. Its main components are albumin in the nucleus and apolipoprotein C on its surface. Chronic cholestatic patients with advanced stages of the underlying disease usually have increased LDL in the presence of LP-X and a decrease in HDL. Cholestatic patients with high triglyceride usually have clear serum due to being rich in LP-Y and LDL.[3]

LP-X is approximately 50 nm in diameter and may contribute to hypercholesterolemia in cholestatic patients by not effectively downregulating hepatic hydroxymethylglutaryl coenzyme A reductase. Bile lipoprotein is a precursor of LP-X, and in cholestasis, it refluxes into the plasma pool and binds to albumin to form LP-X. Serum LP-X usually disappears soon after cholestatic has been relieved. Pseudohyponatremia has also been described in some patients with severe hypercholesterolemia secondary to increased LP-X levels. Therefore, the presence of LP-X should be considered in patients with pseudohyponatremia associated with chronic cholestasis. LP-X possesses strong aggregatory properties and can bind to ALP to produce an LP-X-ALP complex. This complex may be found in cholestasis typically evoked by hepatic malignancy.[3]

As a baseline, lipids should be measured in every patient with PBC, and a careful history should be taken to determine whether the patient or their family has a history of cardiovascular disease. Although hyperlipidemia is not usually a cause for concern in people with PBC, the presence of other risk factors for cardiovascular disease should be considered when choosing cholesterol-lowering drugs. It is safe for people with PBC to consume 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-coA) inhibitors (statins) to lower their cholesterol levels, and they should do so if clinically necessary, such as when they also have metabolic syndrome. Simvastatin not only lowered the levels of total and LDL cholesterol but also lowered the levels of ALP, GGT, and immunoglobulin M in the blood.[3,10] Pravastatin, an HMG-CoA inhibitor reductase, lowers cholesterol and total bilirubin when taken at 20 mg/day and has fewer hepatotoxic side effects.[3]

The new use of fibrates to treat PBC in people who do not respond or only partially respond to ursodeoxycholic acid (UDCA) has the added benefit of lowering lipid levels. Such reductions are completely in line with how these drugs, and PPAR agonists in particular, decrease cholestatic inflammation and decrease bile acid production by CYP7a1. The use of bile acid therapy obeticholic acid is associated with a reduction in lipid levels through selective farnesoid X receptor agonism, but further study is needed.[3]

Diagnosis and Evaluation of Fat-Soluble Vitamin Deficiencies

Individuals with cholestatic liver disease may exhibit symptoms of vitamin deficiency, although these are relatively unusual. In a Mayo Clinical trial examining the efficacy of UDCA in 180 patients with PBC, the proportions of patients with vitamin A, vitamin D, vitamin E, and vitamin K deficiencies were 33.5%, 13.2%, 1.9%, and 7.8%, respectively. Patients with chronic cholestatic disease are more susceptible to developing lipid-soluble vitamin deficiencies due to a lack of bile salts, which are required for vitamin absorption.[3,11]

It is critical to rule out concurrent medical conditions that may worsen malabsorption or fat-soluble vitamin insufficiency. It is recommended to consume vitamins as recommended daily allowance (RDA) in the early stages of the disease (Table 3).[5] Every year, all patients with PBC should have their levels of 25-hydroxyvitamin D, the main vitamin D metabolite, measured in the blood to check for vitamin D deficiency. Once or twice weekly supplementation with 25,000–50 000 IU of vitamin D is recommended to restore vitamin D levels to normal.[3,11]

Symptomatic vitamin A insufficiency is uncommon in cholestasis patients. To determine vitamin A deficiency, serum retinol levels must be measured in patients with cholestasis. Asymptomatic deficits are treated by administering 25 000-50 000 IU two to three times per week or 10 000-20 000 IU orally daily for two months. For 6 months, symptomatic individuals should receive 100 000 U of retinyl palmitate IM every 2 weeks, followed by 45-50 000 U of oral vitamin A supplementation twice weekly.[3,11] The effectiveness of replacement therapy is evaluated by repeating serum vitamin A assays and, if necessary, judging how well the patient adapts to darkness. Patients with chronic cholestatic liver disease, especially those with blood bilirubin levels higher than 2

Table 3. Fat-soluble vitamins: recommended daily allowance (RDA) and oral treatment options for deficiency

Vitamin	RDA	Replacement therapy dose
Vitamin A	3000 IU (man) 2300 IU (woman)	25000-50000 IU twice-three times weekly
Vitamin D	600 IU (51-70 y.o) 800 IU (≥70 y.o)	25000-50000 IU weekly
Vitamin E	33 IU (synthetic) 22 IU (natural)	400 IU/d
Vitamin K	120 mcg (man) 90 mcg (woman)	10 mg parenteral every day for the following 3 days

Adapted from Ahmed et al[3], Lindor et al,[13] and Maillette de Buy Wenniger and Beuers.[14]

mg/dL, must have their vitamin A and D levels checked annually.[13]

Vitamin K deficiency can be clinically significant when severe cholestatic is present. It is characterized by prolonged prothrombin time; therefore, measuring serum vitamin K concentration or coagulation factors II, VII, IX, and X is rarely required. To determine whether prothrombin time improves, an oral trial of 5–10 mg/d of vitamin K should be administered. If so, the patient should continue to take 5 mg of water-soluble vitamin K daily. Active hemorrhage should be treated with intravenous, intramuscular, or subcutaneous vitamin K 10 mg/d for 2–3 days.[14,15]

Diagnosis and Evaluation of Fatigue

Patients with chronic cholestasis commonly experience fatigue]. The level of fatigue in chronic cholestasis is unrelated to the severity of liver disease, and liver transplantation rarely improves this condition. Changes in central serotonergic neurotransmitters may be associated with fatigue. The production of corticotropin-releasing factors and the build-up of magnesium in the globus pallidus are two other hypothesized processes. In PBC, sleep disruptions and postural hypotension alterations in the autonomic nervous system, particularly during the day, are linked to fatigue.[3]

Patients with chronic cholestasis must undergo a comprehensive evaluation of fatigue, excluding other medical conditions, such as anemia, hypothyroidism, electrolyte imbalance, diabetes, and depression. If the previously mentioned conditions are ruled out, fatigue can be confirmed. Currently, there are no specific recommendations for the treatment of chronic cholestatic fatigue. Studies have shown that the administration of 100–200 mg of modafinil per day reduces daytime somnolence and objective fatigue using a variety of scales and questionnaires; however, long-term administration is not recommended because of the possibility of addiction. Avoiding coffee in the late afternoon, which can cause sleep disturbances, and monitoring antihypertensive medications (if any) that exacerbate autonomic nervous system dysfunction may be beneficial. Exercise also contributes to PBC-related fatigue. A study of fluoxetine for the treatment of fatigue in patients with PBC revealed no benefit.[3]

Diagnosis and Evaluation of Steatorrhea

Steatorrhea is a rare medical condition characterized by fecal fat as a result of chronic cholestasis. Patients with decreased intestinal bile acid concentrations typically benefit from the substitution of medium-chain triglycerides (which do not require bile salts for absorption) for long-chain triglycerides in their diets, as well as from a reduction in total fat intake (40–50 g/d). Patients with exocrine pancreatic insufficiency should undergo pancreatic replacement therapy. Patients with celiac disease must eliminate gluten from their diet, whereas those with small intestinal bacterial overgrowth require intermittent broad-spectrum oral antibiotic therapy.[3,10]

Conclusion

Chronic cholestatic disease is a prevalent medical condition that frequently causes complications. Long-standing cholestasis not only increases morbidity and mortality but also affects the patient's quality of life. Pruritus is the most common cholestatic complication of cholestasis. There are no primary skin lesions, but the scratch marks can be made worse by eczema, hyperpigmentation, prurigo nodules, and bacterial infections. Anion exchange resins such as cholestyramine are the first choice for treating cholestatic pruritus. Some other agents for treating pruritus cholestasis are RMP, opioids, and SSRI. Osteoporosis is a chronic cholestatic condition. The evaluation of osteoporosis in chronic cholestatic individuals is the same as in the general population, with BMD being evaluated and WHO criteria and T-score classification being used for diagnosis. Antiresorptive agents such as bisphosphonates are the first-line treatment choice for osteoporosis in patients with chronic cholestasis. Prophylaxis with calcium and vitamin D supplementation is recommended by the National Institute of Health.

Hyperlipidemia is another chronic cholestatic complication in which, as the disease progresses, there is a progressive increase in LDL, a decline in HDL, and the appearance of abnormal lipoprotein particles, such as lipoproteins. Although hyperlipidemia is rarely a concern, the presence of other risk factors for cardiovascular disease should be considered when selecting cholesterol-lowering medications such as statins. Fibrates are another possibility because of their ability to reduce cholesterol levels. Vitamin deficiency can also occur in chronic cholestatic patients, however, it is uncommon in the early stages of the disease, and it is advisable to drink vitamins as recommended by the RDA and to have their vitamin A and D levels evaluated every year. Other medical conditions causing chronic cholestatic complications include fatigue and steatorrhea. Currently, there are no guidelines for the management of chronic cholestatic fatigue.

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Competing Interests

The authors declare no conflict of interest related to this work.

References

1. Shah R, John S. Cholestatic Jaundice (Cholestasis, Cholestatic Hepatitis). Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482279/.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;67(1):145-72. doi: 10.1016/j.jhep.2017.03.022
3. Ahmed A, Mayo MJ. Cholestatic liver disease. In: Complication of Cholestasis. 2nd ed. New York: Springer; 2014. p. 165-88.
4. Kremer AE, Beuers U, Oude-Elferink RP, Pusl T. Pathogenesis and treatment of pruritus in cholestasis. *Drugs* 2008;68(15):2163-82. doi: 10.2165/00003495-200868150-00006
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009;51(2):237-67. doi: 10.1016/j.jhep.2009.04.009
6. Tandon P, Rowe BH, Vandermeer B, Bain VG. The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. *Am J Gastroenterol* 2007;102(7):1528-36. doi: 10.1111/j.1572-0241.2007.01200.x
7. Jones DEJ. Complications of cholestasis. *Medicine* 2002;30(12):67-8. doi: 10.1383/medc.30.12.67.28521
8. Handzlik-Orlik G, Holecki M, Wilczyński K, Duława J. Osteoporosis in liver disease: pathogenesis and management. *Ther Adv Endocrinol Metab* 2016;7(3):128-35. doi: 10.1177/2042018816641351
9. World Health Organization. WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level. Summary Meeting Report. Available from: http://www.who.int/chp/topics/Osteoporosis.pdf.
10. Pithawa AK. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. *Medical Journal Armed Forces India* 2007;63(2):205. doi: 10.1016/S0377-1237(07)80085-2
11. Wariaghli G, Allali F, El Maghraoui A, Hajjaj-Hassouni N. Osteoporosis in patients with primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 2010;22(12):1397-401. doi: 10.1097/MEG.0b013e3283405939
12. Patel N, Muñoz SJ. Bone disease in cirrhosis. *Clin Liver Dis (Hoboken)* 2015;6(4):96-9. doi: 10.1002/cld.498
13. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology* 2009;50(1):291-308. doi: 10.1002/hep.22906
14. Maillette de Buy Wenniger L, Beuers U. Bile salts and cholestasis. *Dig Liver Dis* 2010;42(6):409-18. doi: 10.1016/j.dld.2010.03.015
15. Assis DN. Chronic complications of cholestasis: evaluation and management. *Clin Liver Dis* 2018;22(3):533-44. doi: 10.1016/j.cld.2018.03.014