Pruritus associated with cholestasis

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INTRODUCTION

Cholestasis is seen with many hepatobiliary disorders that produce extrahepatic biliary obstruction and/or intrahepatic biliary disruption. One particularly troublesome symptom associated with cholestasis is pruritus, which can range in severity from mild, to moderate (in which sleep is disturbed), and to extreme (in which the lifestyle of the patient is completely disrupted).

This topic will review the pathogenesis, clinical manifestations, diagnosis, and management of cholestasis-associated pruritus. The disorders associated with cholestasis are discussed elsewhere. (See "Intrahepatic cholestasis of pregnancy" and "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis" and "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis" and "Drug-induced liver injury" and "Clinical manifestations and diagnosis of cholangiocarcinoma" and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis".)

The following discussion is consistent with guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver [1] on the management of primary biliary cholangitis (previously referred to as primary biliary cirrhosis) and cholestatic liver disease, respectively.

ASSOCIATED CONDITIONS

Pruritus may develop in patients with cholestasis due to any cause. It may be seen with primary biliary cholangitis (previously referred to as primary biliary cirrhosis), primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, biliary obstruction, chronic viral hepatitis, cirrhosis, prolonged drug-induced cholestasis, and inherited cholestasis syndromes (eg, progressive familial intrahepatic cholestasis and benign recurrent intrahepatic cholestasis [2]).

The frequency with which pruritus is seen in these conditions is variable [2]:

- Intrahepatic cholestasis of pregnancy: 100 percent (pruritus is a prerequisite for making the diagnosis)
- Primary biliary cholangitis: Up to 80 percent by 10 years
- Primary sclerosing cholangitis: 20 to 40 percent of patients at presentation, increasing as the disease progresses
- Malignant biliary tract obstruction: 45 percent
- Chronic viral hepatitis: 20 percent
- Nonmalignant biliary tract obstruction: 17 percent
- Cirrhosis: 7 percent

PATHOGENESIS

The pathogenesis of pruritus in cholestasis is unknown, but several hypotheses have been proposed, including bile acid accumulation, activation of specific neuronal pathways, and elevation in lysophosphatidic acid levels [3-5].

Bile acids — One theory proposes that elevated levels of bile acid in the skin act as pruritogens. Observations in favor of this theory include the recovery of bile acids from the skin surface of affected patients [6], although the reliability of the methods used to detect the bile acids is uncertain. Other studies have found that administering bile acids can induce pruritus [7,8].

However, there are three observations that are not consistent with a primary role for bile acids as the cause of pruritus:

- The occasional subsidence of pruritus despite ongoing cholestasis and persistence of elevated plasma bile acid levels [9]
- The absence of pruritus in many patients with cholestasis and elevated plasma bile acid levels [9]
- The apparent lack of correlation between the presence or severity of pruritus and concentrations of bile acids in skin of patients with chronic cholestasis in the most

carefully done study that investigated this question [10]

Furthermore, cholestyramine and colestipol, agents used to treat the pruritus of cholestasis, also ameliorate pruritus in patients with uremia and polycythemia vera, conditions not associated with bile salt retention. (See 'Bile acid sequestrants' below.)

A related hypothesis implicates elevated plasma bile acids via hepatocyte toxicity, rather than their effect on nerve endings [11]. The detergent bile acids alter hepatocyte membranes, permitting the leakage of hepatocyte contents (some of which are pruritogens) into the bloodstream.

Endogenous opioids — There is increasing evidence for an important role for endogenous opioids in the pathogenesis of cholestatic pruritus [12]. The administration of opioid drugs with agonist activity at the mu opioid receptor can produce pruritus in normal individuals, presumably by a central action. More importantly, endogenous opioid levels are elevated (via an uncertain mechanism) in patients with chronic liver disease [13,14], and many reports have shown a reduction in cholestatic pruritus in patients treated with opioid antagonists [12,15-17]. (See 'Opioid antagonists' below.)

Lysophosphatidic acid — Studies suggest an important role for lysophosphatidic acid (LPA) in cholestatic pruritus [18-20]. LPA is a phospholipid that is formed by the action of autotaxin, which cleaves a choline group from lysophosphatidylcholine. In one study, compared with controls, patients with cholestatic pruritus had significantly increased serum concentrations of LPA and autotaxin activity [18]. In addition, injection of LPA induced a scratch response in mice. (See 'Rifampin' below.)

CLINICAL MANIFESTATIONS

Pruritus in patients with cholestasis may be generalized or localized (particularly to the palms of the hands and soles of the feet) [2]. The intensity of the pruritus is variable and it can wax and wane spontaneously. The severity does not correlate with the severity of the underlying liver disease. Pruritus is often worse at night and may be exacerbated by psychologic stress. Females who are premenstrual may also experience a worsening of symptoms. Cool temperatures often lead to improvement. Long-standing scratching may result in excoriations, folliculitis, prurigo nodularis, and lichenification.

Pruritus can have a profound effect on a patient's quality of life, resulting in sleep deprivation and emotional disturbances (including suicidal ideation in some patients) [2].

Quantifying the severity of pruritus can be difficult but is important when evaluating the efficacy of medical therapy. Investigators have developed a scratching activity monitoring system that allows for recording of scratching behavior independent from gross body movement, thereby allowing for the inclusion of behavioral methodology in clinical trials of pruritus [21]. Nevertheless, clinical trials have generally been small and used varying scales for measuring pruritus limiting comparison among them [22].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis for causes of pruritus is long. However, a presumptive diagnosis of cholestasis-associated pruritus can be made in a patient with cholestasis who complains of itching. An extensive evaluation is generally not required, provided the cause of the cholestasis is known, though patients should have a skin examination to look for evidence of dermatologic disorders associated with pruritus (eg, atopic dermatitis or contact dermatitis). In addition, uremic pruritus should be considered in patients with end-stage kidney disease. If the cause of the cholestasis is not known, the patient should undergo additional evaluation with laboratory tests and imaging studies. (See "Pruritus: Etiology and patient evaluation" and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated alkaline phosphatase'.)

NATURAL HISTORY

The intensity of pruritus typically fluctuates over time (both within the day and over longer periods of time). It may lessen with the development of end-stage liver disease. It may also improve with time in patients with primary biliary cholangitis (previously referred to as primary biliary cirrhosis). In females with intrahepatic cholestasis of pregnancy, pruritus often worsens as the pregnancy progresses and then typically resolves within a few days of delivery [23]. Some patients develop severe, refractory pruritus requiring liver transplantation. (See 'Pruritus refractory to standard treatment' below.)

MANAGEMENT

Treatment of the underlying disorder — The first step in treating patients with cholestasis-associated pruritus is to treat the underlying disease, if possible. The specific treatment will depend on the cause of the cholestasis. Some of the disease-specific treatments include:

- Primary biliary cholangitis (previously referred to as primary biliary cirrhosis): Ursodeoxycholic acid
- Primary sclerosing cholangitis: Endoscopic treatment of dominant strictures
- Malignant extrahepatic biliary obstruction: Bile duct stenting
- Drug-induced cholestasis: Discontinuation of the offending medication

Treatment of pruritus — The treatment of pruritus depends on the severity of symptoms. If symptoms are mild, nonspecific measures (eg, emollients) may help. Moderate to severe pruritus is treated with pharmacologic therapy (eg, cholestyramine). Severe, refractory pruritus may require liver transplantation.

Mild pruritus — If the pruritus is mild, treatments such as warm baths and emollients may help. Antihistamines may also be helpful, particularly for patients with insomnia. However, these measures often fail when the pruritus is moderate to severe.

Moderate to severe pruritus

General approach — For patients with moderate to severe pruritus who do not respond to nonspecific measures, we begin pharmacologic therapy.

For patients who do not have primary biliary cholangitis or intrahepatic cholestasis of pregnancy we do the following:

- We initially treat with a bile acid sequestrant such as cholestyramine (total daily dose of 4 to 16 grams). (See 'Bile acid sequestrants' below.)
- If the bile acid sequestrant does not provide adequate, relief we switch to rifampin (150 to 300 mg twice daily). (See 'Rifampin' below.)
- If symptoms persist, we then switch to an opioid antagonist, such as naltrexone (12.5 to 50 mg/day). (See 'Opioid antagonists' below.)
- Switching to sertraline (75 to 100 mg daily) or phenobarbital 90 mg at bedtime can be tried if other measures fail. Phenobarbital has the disadvantage of causing somnolence during the first few weeks of use. (See 'Sertraline' below and 'Pruritus refractory to standard treatment' below.)

For treatment of pruritus in patients with primary biliary cholangitis, in addition to cholestyramine, we suggest treatment with ursodeoxycholic acid. We start with a low dose (eg, 200 to 300 mg daily) and then over the next few weeks gradually increase the dose to 13 to 15 mg/kg per day given in two to three divided doses. Bile acid sequestrants should be given two

to four hours before or after ingestion of ursodeoxycholic acid (UDCA). For patients with primary biliary cholangitis who do not respond to ursodeoxycholic acid alone, bezafibrate can be used in combination with ursodeoxycholic acid [24,25]. (See "Overview of the management of primary biliary cholangitis", section on 'Pruritus'.)

Treatment in females with intrahepatic cholestasis of pregnancy must take into account potential adverse effects of the treatment on the fetus. UDCA has been studied in females with intrahepatic cholestasis of pregnancy and is well-tolerated and safe. Its use has been associated with relief of pruritus, decreased levels of endogenous bile acids, normalization of alanine aminotransferase levels, and improved fetal outcomes [26-30]. Cholestyramine and antihistamines are often ineffective and are not well tolerated in this population [23,31]. (See "Intrahepatic cholestasis of pregnancy", section on 'Maternal treatment'.)

Bile acid sequestrants — The bile acid resins cholestyramine and colestipol are effective first-line agents in the management of moderate to severe cholestatic pruritus based on their favorable safety profile and clinical experience [32]. The effective dose of cholestyramine ranges from 4 to 16 grams per day. Treatment typically begins with two 4-gram doses daily, with additional doses being added if needed. In patients who are also taking UDCA, bile acid sequestrants should be given two to four hours before or after ingestion of UDCA. Efficacy may be increased by administering a dose before and a dose after breakfast in patients with an intact gallbladder to enhance the excretion of the pruritogens, which presumably accumulate in the gallbladder during the overnight fast. If symptoms persist, the dose can be titrated upward by giving a dose after lunch and, if needed, a dose after dinner.

These drugs are nonabsorbable, basic polystyrenes that bind anions in the gut lumen, including bile acids. They lower bile acid levels by inhibiting the reabsorption of bile acids by approximately 90 percent. However, binding of bile acids alone is unlikely to explain their benefit, since a potent bile acid sequestrant (colesevelam) was not effective for cholestatic pruritus in a randomized trial [33]. They also decrease pruritus in noncholestatic disorders, such as uremia and polycythemia vera, suggesting that these resins bind other pruritogens. This may in part be due to the induction of cholecystokinin release, which is an endogenous anti-opioid [34,35].

There have been few randomized trials of cholestyramine for cholestasis-associated pruritus [22]. Early studies suggested 80 to 85 percent of patients responded, either completely or partially, with a response maintained for 6 to 36 months. Improvement is often seen within a few weeks of starting treatment [2].

Medication adherence can be a significant problem with the use of bile acid resins. These drugs are unpalatable, induce constipation, and can interfere with the absorption of a number of medications including UDCA, digoxin, warfarin, propranolol, and thiazide diuretics. They can also lead to fat malabsorption and vitamin K deficiency. As a result, patients should be monitored for vitamin K deficiency while receiving bile acid resins.

Rifampin — Several reports have demonstrated improvement in cholestatic pruritus with rifampin (also known as rifampicin) [22,36-38]. It is given as 150 to 300 mg twice daily. In a meta-analysis of five randomized crossover trials with 61 patients, during treatment with rifampin, 47 patients (77 percent) reported complete or partial resolution of pruritus, whereas 12 patients (20 percent) reported complete or partial resolution of pruritus while receiving placebo or alternative medication [38].

Rifampin is a potent agonist of the pregnane X receptor (PXR), which mediates many detoxification and hepatobiliary processes. In addition, rifampin reduced autotaxin expression at the transcriptional level in a PXR-dependent manner in a study using human hepatoma cells [20]. This may explain the molecular mechanisms behind the anti-pruritogenic action of rifampicin in patients with pruritus associated with cholestasis. (See 'Lysophosphatidic acid' above.)

Adverse effects of rifampin include nausea, decreased appetite, hemolytic anemia, renal failure, and hepatitis [22,39]. Because of the risk of hepatitis, caution should be exercised with rifampin use in cholestatic conditions, and patients should have their serum aminotransferase monitored at regular intervals (eg, every three months).

Opioid antagonists — Opioid antagonists such as intravenous naloxone (given as a bolus of 0.4 mg followed by 0.2 mcg/kg per minute for 24 hours), oral nalmefene (60 to 120 mg daily), and oral naltrexone (12.5 to 50 mg daily) are often associated with substantial relief of cholestatic pruritus [15,22,40-43]. Opioid antagonists should not be used in patients receiving opioid-containing medications or in patients with acute hepatitis, liver failure, or severe liver dysfunction [39].

In a randomized crossover trial with 29 patients, naloxone led to a 27 percent reduction in scratching activity and to a significant reduction in the perception of pruritus [40]. Similarly, a study of 16 patients randomly assigned to receive naltrexone or placebo found that the former was associated with a significant improvement in daytime itching (change in pruritus score -54 versus 8 percent), as well as nighttime itching (-44 versus 7 percent) [41]. Persistent benefits were observed for at least two months in a third randomized crossover trial with 20 patients

[43]. Nine patients had a >50 percent decrease in pruritus, and pruritus disappeared completely in five.

Opioid antagonists are generally well tolerated with the exception of a self-limited opioid withdrawal-like syndrome that usually resolves spontaneously within two days [43]. This problem may be more prominent with nalmefene, which is currently only available for experimental use [42]. The likelihood of a withdrawal syndrome may be decreased with a cautious initial intravenous infusion (such as naloxone starting at 0.002 micrograms per kg/min, gradually increasing until reaching a therapeutic dose) followed by oral therapy [44]. In addition, opioid antagonists may lead to uncontrolled pain in patients who have various underlying causes of pain (eg, postherpetic neuralgia) [45]. As the role of endogenous opioids for cholestatic pruritus becomes better defined, the use of these agents, particularly the oral formulations, may become more widespread.

Sertraline — Case series and a small controlled trial have suggested a possible benefit from selective serotonin reuptake inhibitors. Sertraline (75 to 100 mg daily) was effective in a retrospective analysis of a group of patients with primary biliary cholangitis who were participating in a trial of UDCA with and without methotrexate [46], and in a small randomized crossover trial of patients with pruritus due to various forms of liver disease [47]. Paroxetine was beneficial in a separate report of patients with severe non-dermatologic pruritus (most of whom had non liver disease-related causes) [48].

Antihistamines — Antihistamines are commonly used for the treatment of pruritus in patients with cholestatic liver disease, though studies looking at their efficacy are lacking. Because of their sedating effects, antihistamines may be beneficial in patients who have insomnia as a result of their pruritus [49].

Ursodeoxycholic acid — UDCA is effective for treating pruritus in patients with intrahepatic cholestasis of pregnancy, and it may be effective for treating pruritus in primary biliary cholangitis where it is also used as part of the standard treatment for primary biliary cholangitis. However, the effect of UDCA on pruritus due to cholestatic disorders is unclear [50]. In terms of treating pruritus, we reserve UDCA for the treatment of patients with intrahepatic cholestasis of pregnancy or primary biliary cholangitis. UDCA is given as 13 to 15 mg/kg per day (given in two to three divided doses). (See "Intrahepatic cholestasis of pregnancy", section on 'Ursodeoxycholic acid' and "Overview of the management of primary biliary cholangitis", section on 'Initial therapy'.)

UDCA is a naturally occurring dihydroxy bile acid that, when administered exogenously, changes the bile acid pool to a more hydrophilic mix [51,52]. It is unclear if this effect is due to

competition for intestinal absorption of endogenous bile acids or to increased hepatic clearance of endogenous bile acids.

In females with intrahepatic cholestasis of pregnancy, UDCA is well-tolerated and safe. Its use has been associated with relief or pruritus, decreased levels of endogenous bile acids, normalization of alanine aminotransferase levels, and improved fetal outcomes [26-30]. (See "Intrahepatic cholestasis of pregnancy", section on 'Ursodeoxycholic acid'.)

Two large trials in primary biliary cholangitis showed no improvement in pruritus at a dose of 13 to 15 mg/kg per day [53,54]. By comparison, high-dose therapy (30 mg/kg per day in three divided doses) in another report led to relief of itching [55]. In the latter study, pruritus disappeared in six of seven patients within one month. Until more data become available, we do not recommend high-dose therapy for patients with primary biliary cholangitis.

Pruritus refractory to standard treatment — In patients with moderate to severe pruritus that fails to improve adequately with standard treatment, consideration should be given to alternative treatments. Switching to sertraline or phenobarbital at bedtime can be tried if other measures fail. Phenobarbital has been effective in case series [56,57]. It can be given as 90 mg at bedtime, although it has the disadvantage of causing somnolence during the first few weeks of use. If medical treatments fail and the pruritus is severe, liver transplantation may be the only effective therapy.

Novel ileal bile acid transport (IBAT) inhibitors may be effective in reducing the severity of pruritus in patients with cholestasis by interrupting enterohepatic circulation of bile acids. In a randomized phase II crossover trial, 22 patients with pruritus associated with primary biliary cirrhosis were assigned to a selective inhibitor of human IBAT (GSK2330672) or placebo for two weeks [58]. Treatment with GSK2330672 was not associated with any serious side effects. Diarrhea was the most frequent treatment-related adverse event and was significantly higher in the treatment group as compared with placebo (7 versus 1) but did not require dose reduction or discontinuation. Treatment with GSK2330672 resulted in a significant reduction in total and conjugated bile acids and pruritus. However, larger studies of longer duration are needed to assess the efficacy of GSK2330672 in the treatment of pruritus in cholestasis.

Several other treatments have only been evaluated in case series, but their role in the routine treatment of cholestasis-associated pruritus is unclear:

- Phototherapy with ultraviolet light (UV-B) has been helpful in case reports [59-61]. The mechanism is unknown, although hypotheses include an alteration in skin sensitivity to pruritogens or a modification in bile salt turnover by mobilizing skin bile salts. In our

experience, phototherapy has been unsuccessful in more than 80 percent of patients with primary biliary cholangitis who failed to respond to cholestyramine.

- Some studies have demonstrated relief of pruritus following plasmapheresis in patients with cholestasis [62-64]. However, clinical experience has been mixed. This technique is too cumbersome and expensive for routine use but may have a role when all else fails, particularly when a more definitive treatment is anticipated, such as in patients awaiting liver transplantation.

- Nasobiliary drainage was effective in a series of 27 patients who underwent 29 nasobiliary drainage procedures [65]. The median duration of nasobiliary drainage was seven days, and pruritus improved following 26 of the procedures (90 percent). However, 31 percent of procedures were associated with mild post-endoscopic retrograde cholangiopancreatography pancreatitis.

- Propofol was given to three patients at subhypnotic doses via intravenous infusion [66]. Marked improvement in pruritus was noted without disabling sedation. The proposed mechanism was inhibition of ventral and dorsal spinal nerve roots modulated by endogenous opioid-like ligands.

- Androgens (such as norethandrolone, methyltestosterone, and stanozolol) increase serum bile acids and worsen jaundice, yet they paradoxically relieve pruritus in some patients with cholestasis [67]. How this occurs is not known, but multiple side effects limit the use of these drugs.

- Delta-9-tetrahydrocannabinol (Marinol) was helpful in a case series of three patients [68].

- The Molecular Adsorbent Recirculating System (a hemofiltration device) has been effective in case series [69-72].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Primary biliary cholangitis".)

SUMMARY AND RECOMMENDATIONS

- Pruritus may develop in patients with cholestasis due to any cause, including primary biliary cholangitis (previously referred to as primary biliary cirrhosis), primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, biliary obstruction, chronic viral hepatitis, cirrhosis, prolonged drug-induced cholestasis, and inherited cholestasis syndromes. (See 'Associated conditions' above.)

- Pruritus in patients with cholestasis may be generalized or localized (particularly to the palms of the hands and soles of the feet). The intensity of the pruritus is variable and it can wax and wane spontaneously. The severity does not correlate with the severity of the underlying liver disease. (See 'Clinical manifestations' above.)

- A presumptive diagnosis of cholestasis-associated pruritus can be made in a patient with cholestasis who complains of itching. An extensive evaluation is generally not required, provided the cause of the cholestasis is known, though patients should have a skin examination to look for evidence of dermatologic disorders associated with pruritus (eg, atopic dermatitis or contact dermatitis). (See 'Diagnosis and differential diagnosis' above.)

- The treatment of choice for pruritus associated with cholestasis is correction of the underlying hepatobiliary disease, when possible. If the underlying hepatobiliary disease cannot be corrected, treatment is aimed at the pruritus itself. The treatment chosen will depends on the severity of symptoms and the underlying disease:

  - For mild pruritus, we suggest general measures such as warm baths with or without an antihistamine (**Grade 2C**). (See 'Mild pruritus' above.)

  - For patients with primary biliary cholangitis and moderate to severe pruritus, we suggest treatment with a bile acid sequestrant rather than an alternative medication (such as rifampin or an opioid antagonist) (**Grade 2B**). We also recommend treatment with ursodeoxycholic acid (UDCA) rather than treating with a bile acid sequestrant alone (**Grade 1A**). UDCA may improve pruritus in these patients and delays the progression to end-stage liver disease, enhances survival, and is well-tolerated. Bile acid sequestrants should be given two to four hours before or after ingestion of UDCA.

  - In females with intrahepatic cholestasis of pregnancy and moderate to severe pruritus, we suggest treatment with UDCA (**Grade 2B**). UDCA has been studied in females with intrahepatic cholestasis of pregnancy and is well-tolerated and safe. Its use has been associated with relief or pruritus, decreased levels of endogenous bile acids, normalization of alanine aminotransferase levels, and improved fetal outcomes. (See 'Ursodeoxycholic acid' above and "Intrahepatic cholestasis of pregnancy", section on 'Ursodeoxycholic acid'.)

- For patients with moderate to severe pruritus who do not have primary biliary cholangitis or intrahepatic cholestasis of pregnancy, we suggest treatment with a bile acid sequestrant such as cholestyramine or colestipol (**Grade 2B**). (See 'Bile acid sequestrants' above.)

  For patients who do not respond to or do not tolerate a bile acid sequestrant, we suggest the following approach (**Grade 2C**):

  - First, we switch to rifampin. (See 'Rifampin' above.)

  - If symptoms persist, we then switch to an opioid antagonist, such as naltrexone. Opioid antagonists are generally well tolerated with the exception of a self-limited opioid withdrawal-like syndrome that usually resolves spontaneously within two days. Opioid antagonists should not be used in patients receiving opioid-containing medications or in patients with acute hepatitis, liver failure, or severe liver dysfunction. (See 'Opioid antagonists' above.)

  - Switching to sertraline or phenobarbital at bedtime can be tried if other measures fail. Phenobarbital has the disadvantage of causing somnolence during the first few weeks of use. (See 'Sertraline' above and 'Pruritus refractory to standard treatment' above.)

- If medical treatments fail and the pruritus is severe, biliary diversion and liver transplantation may be the only effective therapy. (See 'Pruritus refractory to standard treatment' above.)

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