Complications of cholestasis

Vinod S Hegade
David EJ Jones

Abstract

Cholestasis (impairment of, or reduction in, bile flow) can both predispose to the development of chronic liver disease and result in its own specific symptoms. The severity of cholestatic symptoms (which themselves often impair quality of life) is typically independent of the severity of the underlying liver disease, the link with cholestasis therefore frequently being missed. The most characteristic symptoms of cholestasis are pruritus and fatigue, the former being the most responsive to treatment. After excluding surgically or endoscopically treatable biliary tree obstruction, the first-line treatment for cholestatic pruritus is colestyramine. Rifampicin and the oral opiate antagonist naltrexone are effective second-line treatments with a good evidence base. There is currently no licensed or recommended therapy for fatigue and the approach is largely supportive. Osteoporosis can complicate cholestatic liver disease, although the risk has previously been overstated. The highest additional cholestasis-associated risk is seen in male patients, in patients taking corticosteroids and in the most severely cholestatic patients. Patients should undergo formal bone mineral density screening, and bisphosphonate treatment is highly effective.

Keywords Cholestasis; complications; fatigue; MRCP; osteoporosis; pruritus

Key points

- Symptoms are common in cholestatic disease, important to patients but frequently neglected by clinicians
- Pruritus can be severe, but effective treatments are available that are described in clinical guidelines; if significant it should always be treated
- Fatigue, frequently accompanied by mild cognitive impairment, is the most common symptom in cholestasis and there is no licensed therapy. Management should be supportive, including working with patients on coping strategies
- Social isolation can be common if there are significant cholestatic symptoms and can compound impairment of quality of life. Avoiding isolation should be a part of patients' coping strategies

Introduction

The term 'cholestasis' refers to impairment of, or reduction in, bile flow. This can arise from blockage within the biliary tree (obstructive cholestasis) or impairment of bile secretion by hepatocytes into the bile canaliculi (non-obstructive or intrahepatic cholestasis). Chronic cholestasis results in problems resulting from:

- complications of the predisposing cholestatic disease
- complications associated with chronic liver disease resulting from the presence of cholestasis
- specific clinical features and complications of cholestasis.

The first two issues are beyond the scope of this contribution.

Vinod S Hegade ***PhD MRCP*** *is a Consultant Hepatologist at the Leeds Teaching Hospitals Trust, UK. Competing interests: VSG has received research funding from GSK.*

David EJ Jones ***PhD FRCP OBE*** *is a Professor of Liver Immunology at Newcastle University and Honorary Consultant Hepatologist at the Freeman Hospital, Newcastle Upon Tyne, UK. Competing interests: DEJJ has received research funding from GSK, Pfizer and Intercept, and consultancy fees from GSK, Novartis, Intercept and Falk.*

Pruritus

Itch is the archetypal symptom of cholestasis, potentially occurring at all stages of cholestatic liver disease (even in patients who are not jaundiced). Its underpinning mechanisms remain unclear, although evidence suggests key roles for autotaxin and lysophosphatidic acid.[1] The responses to key therapeutic agents also suggest roles for 'toxic' bile acids and endogenous opiates, which are known to be elevated in cholestasis. In the clinical setting, the severity of pruritus can be effectively assessed using numerical scoring systems or visual analogue scales (e.g. 0–10 ratings).

In attempting to provide relief, the first approach is, if possible, reversal of the underlying cholestasis. Treatment of biliary obstruction using endoscopy, interventional radiology and/or surgery generally 'cures' pruritus. In intrahepatic cholestasis, symptomatic management should be tailored to severity of the itch. Topical therapy with aqueous cream and 1% menthol can be sufficient for mild, localized itching. For more severe, generalized itch, guidelines recommend using colestyramine as first-line therapy.[2] Rifampicin and naltrexone should be used as second- and third-line agents, respectively. Table 1 suggests a protocol for the treatment of itch in cholestasis. Evidence from large population cohorts with primary biliary cholangitis, one of the most common cholestatic diseases, suggest an underuse of therapy for pruritus and surprisingly high levels of residual symptoms.[3]

The hydrophilic bile acid ursodeoxycholic acid (UDCA), which acts as a choleretic agent, displacing potentially toxic bile acids from the recirculating bile acid pool, is widely used to reduce secondary liver damage in forms of cholestatic liver disease (at a weight adjusted dose of 12–16 mg/kg). However, UDCA has not been shown to be effective in treating pruritus and can occasionally cause it or make it worse; this should be remembered when pruritus is difficult to control in a patient taking UDCA.

Liver transplantation is highly effective as a treatment for cholestatic pruritus and should be considered in appropriate

A suggested approach to the management of pruritus in cholestatic disease

1 Exclude other systemic and dermatological causes. Note that secondary skin excoriation is common in pruritus secondary to systemic disease. The presence of skin lesions in a patient with pruritus does not necessarily indicate a dermatological aetiology

2 Explore definitive approaches to therapy (e.g. reversal of stasis secondary to biliary stricture). Where possible (which depends on the aetiology of cholestasis), such approaches are always more valuable than symptom management alone

3 In patients taking UDCA, consider a trial off therapy as UDCA is known to cause 'paradoxical itch'. If the patient is not taking UDCA, consider its use in an adequate dose (12–16 mg/kg/day)

If there is no response:

4 Add colestyramine at a dose of 4–8 g daily, preferably before and after breakfast so that the maximum effect coincides with release during the first meal of the day of bile acids produced overnight and stored in the gallbladder. Always separate it from UDCA dosing by at least 3 hours. If needed, improve tolerability by adding fruit juice

If there is no response:

5 Consider rifampicin. Start at 150 mg daily and monitor liver function tests (LFTs) weekly for a month. If necessary, increase in increments of 150 mg to a maximum daily dosage of 600 mg. Note that rifampicin often causes elevated transaminases and, rarely, leads to severe liver dysfunction (generally reversible on stopping therapy). Regular monitoring of LFTs is recommended. Note also that the dose of rifampicin used for pruritus is lower than the recommended dose for anti-microbial indications, and the introduction tapered, because of the hepatotoxicity risk.

If there is no response or rifampicin is not tolerated:

6 Consider opiate antagonist therapy. If the patient is taking opiates, stop them if possible (allowing for a washout period) or substitute alternative analgesia. The standard therapeutic approach is oral naltrexone 25–50 mg daily. Induction of treatment can be complicated by opiate withdrawal reactions (abdominal pain, goosebumps, nightmares, high blood pressure, tachycardia, depersonalization). If the patient is not overtly cholestatic (jaundiced), try a single dose of naltrexone 25 mg, having warned them about the possible reaction. If no reaction is seen, continue with 25 mg/day for 4 weeks with weekly LFT checking. Increase the dose if needed by 12.5 mg every 3–7 days Alternatively, admit the patient electively for intravenous naloxone induction (start at 0.002 micrograms/kg/minute and increase to 0.2 micrograms/kg/minute over 72 hours) and then start naltrexone 25 mg daily with monitoring.

If there is no response:

7 Consider invasive interventions such as ultraviolet B phototherapy, endoscopic nasobiliary drainage, plasmapheresis and/or a molecular adsorbent recirculating system. Offer participation in continuing clinical trials of novel drug therapy

If there is no response or treatment is not tolerated:

8 Consider liver transplantation

Notes

- Routine use of antihistamines is not recommended, but a sedative antihistamine can be given to patients with insomnia secondary to nocturnal pruritus
- Progression to treatment level 5 and above represents a significant step-up in treatment intensity (and adverse effects). Make sure all earlier approaches have been adequately explored before taking this step
- Use of rifampicin and naltrexone should be restricted to the secondary and tertiary care settings

Table 1

patients in whom all medical approaches to therapy have failed, even in the absence of liver synthetic dysfunction.

Osteoporosis

The cause of osteoporosis in cholestatic liver disease is uncertain but three factors appear to be associated with a significant excess risk:

- male gender
- intercurrent therapy associated with osteoporosis (particularly corticosteroid therapy)
- end-stage disease, before and during the first year after liver transplantation.

Table 2 outlines a suggested protocol for the management of osteoporosis in cholestasis.[4]

Fatigue

Fatigue is common in chronic cholestatic diseases such as PBC and primary sclerosing cholangitis.[5] Specific quality-of-life measures validated for use in cholestatic liver disease have helped to highlight the extent of the problem, but treatment options are currently limited. Causes other than cholestasis should be explored and treated; these include anaemia, hypothyroidism, vitamin D deficiency, depression and sleep disorder. Several studies in PBC have suggested a correlation between severity of fatigue and severity of itch (particularly night-time itch).

Treating itch in fatigued patients can reduce fatigue. In PBC patients with fatigue associated with significant daytime somnolence, oral modafinil in doses 100–200 mg/day has been shown to significantly decrease sleep abnormalities and fatigue. Antioxidant vitamins (ubiquinone 100 mg/day) and staged exercise programmes can also be beneficial. Fatigue can be associated with significant social isolation, which can compound the impact on quality of life.

Fat malabsorption and its sequelae

The possibility of fat malabsorption, particularly deficiency of fat-soluble vitamins (A, D, E, K), should be considered in all patients with overt cholestasis. Parenteral vitamin K should be

A suggested approach to the management of osteoporosis in cholestatic disease

Monitoring

- Given the importance of risk factors unrelated to cholestasis, undertake a full risk assessment
- At diagnosis/referral, offer bone mineral density (BMD) assessment to all patients with chronic cholestatic disease
  T-score < -2.5 — offer therapy (group 1 below) and repeat BMD assessment in 1 year
  T-score $= 0$ to -2.5 — institute prevention (group 2 below) and repeat BMD assessment in 1 year
  T-score >0 — institute prevention (group 2 below) and repeat BMD assessment in 5 years
- The lack of clear correlation between improvement in BMD and reduction in fracture rate should be borne in mind
- All patients with cholestasis who have a fracture should undergo annual BMD assessment and be considered for group 1 therapy

Therapy

Group 1 (osteoporotic by World Health Organization (WHO) criteria (T-score < -2.5))

- Recommend appropriate lifestyle modifications (e.g. stopping smoking, increase exercise); calcium and vitamin D supplementation if there is reasonable suspicion of deficiency
- Assess gonadal function. If hypogonadism is present, consider hormone replacement therapy. Note concerns about the use of sex hormone therapy in male patients with chronic liver disease at risk of primary hepatocellular carcinoma
- Bisphosphonate therapy according to local practice (agents with once-weekly dosing regimens are preferred in our clinic)

Group 2 (osteopenic or normal by WHO criteria)

- As for group 1, but without bisphosphonate therapy

Table 2

given to every patient with cholestatic liver disease before invasive procedures. The potential benefit of parenteral vitamin D should be remembered in patients with cholestasis-associated metabolic bone disease. However, the previous practice of giving parenteral vitamin A and D to non-jaundiced patients is now regarded as inappropriate, with the possible exception of patients requiring prolonged colestyramine therapy. ◆

KEY REFERENCES

1 Beuers U, Kremer AE, Bolier R, Elferink RP. Pruritus in cholestasis: facts and fiction. *Hepatol* 2014; **60:** 399–407.

2 Beuers U, Boberg KM, Chapman RW, et al. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; **51:** 237–67.

3 Hegade VS, Mells GF, Fisher H, et al. Pruritus in primary biliary cholangitis is common and under-treated: results from 2194 patients in the UK-PBC cohort. *Clin Gastroenterol Hepatol* 2019; **17:** 1379–87.

4 Collier JD, Ninkovic M, Compston JE. Guidelines on the management of osteoporosis associated with chronic liver disease. *Gut* 2002; **50**(suppl 1)**:** i1–9.

5 Dyson JK, Beuers U, Jones DEJ, et al. Primary sclerosing cholangitis. *Lancet* 2018; **391:** 2547–59.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 42-year-old woman presented with itch. She had primary biliary cirrhosis and was taking ursodeoxycholic acid (UDCA) at a dose of 13 mg/kg. She had been taking colestyramine at a dose of 8 g daily but this had not helped her itch.

What would be the most reasonable next step in treatment?

A Rifampicin
B Antihistamine (ideally non-sedating)
C Referral for consideration of transplantation
D Naltrexone
E Increase the UDCA dose to 20 mg/kg

Question 2

A 35-year-old woman presented with fatigue, which she described as 'brain fog'. This was making her working life very difficult. She had been found to have PBC.

What is the best advice to give her?

A That this is unlikely to be related to her PBC as PBC fatigue is typically muscular or peripheral in nature
B To adjust her working pattern to focus key activities in the morning
C To consider stopping working
D To try modafinil therapy
E To seek counselling as the fatigue is likely to be a manifestation of depression

Question 3

A 48-year-old man presented with a fracture after significant trauma. He had long-term cholestasis and a 30 pack–year smoking history.

On clinical examination, his body mass index was 26 kg/m^2.

What advice should he be given about osteoporosis?

A Not to worry about it as he is male and thus not at risk
B To stop smoking
C To avoid exercise as it puts him at risk of further trauma
D To lose weight to stop putting additional stress on the hips and spine
E To take bisphosphonates