

Itch and liver:

management in primary care

INTRODUCTION

Pruritus can be defined as 'an unpleasant sensation that causes the need to scratch.'¹ Although it is most commonly seen in skin diseases it can occur as a consequence of systemic conditions and the possibility of the presence of such conditions should be considered in any patient presenting with pruritus in the absence of rash. Pruritus can be a feature of renal failure, haematological diseases (including lymphoma, leukaemia, and myeloproliferative disorders),² and of liver diseases in which there is an element of cholestasis (impaired bile secretion). Pruritus in liver diseases can often be a debilitating symptom causing significant impairment in quality of life. Not all patients with liver disease develop pruritus and its prevalence varies depending on the underlying cause of liver disease. It is more common in conditions characterised by bile duct inflammatory destruction than in those characterised by hepatocellular injury.³ For example, the prevalence of pruritus is high in autoimmune liver diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and biliary obstructive diseases secondary to benign (stones/strictures) or malignant diseases (for example, carcinoma of head of pancreas). It can also be seen in patients with chronic viral hepatitis (mainly hepatitis C) and drug-induced liver injury (DILI). In comparison, pruritus is relatively uncommon in alcohol-induced liver diseases (ALD) and non-alcoholic fatty liver disease (NAFLD).

Patients with pruritus often seek treatment from their GPs but studies have shown there is lack of awareness among clinicians in relation to pruritus associated with liver diseases.⁴ GPs are able to initiate treatments recommended by the guidelines so they and their patients would benefit from a knowledge of the condition and the understanding of currently available therapies.

PRESENTATION

Pruritus can develop at any stage of cholestatic liver disease and it should be

particularly noted that severity of cholestatic itch is independent of the duration, biochemical severity, and histological stage of the underlying liver disease. In PBC, the liver condition most typically associated with pruritus, patients with pruritus typically have biochemical abnormality characterised by chronically (>6 months) elevated serum alkaline phosphatase (ALP). However, it is possible to see pruritus in patients with early PBC with completely normal liver function tests (LFT). Healthcare providers should be mindful of this lack of correlation between itch and biochemical abnormality and a potential liver diagnosis should not be dismissed in a symptomatic patient with normal LFT. In patients with itch and normal LFT a positive antimitochondrial antibody (AMA) test should raise the suspicion of PBC.

Pruritus in cholestasis has a number of unique features that should prompt appropriate investigations and diagnosis, which will help alert the clinician to a liver aetiology (as opposed to dermatological or other systemic causes). It tends to be generalised, predominantly affecting limbs and in particular palms and soles (palmoplantar pruritus). It is typically worse late in the evening and at night, and usually exacerbated by heat (including hot baths), menstrual period, hormone replacement therapy, early pregnancy, and contact with wool.⁵ Classical histamine-induced skin changes such as erythema, urticaria, and flares are not seen in patients with cholestatic pruritus. Characteristically, there is absence of skin lesions but intense scratching can result in secondary skin lesions including excoriations, folliculitis, and lichenification, which can occasionally lead to the mistaken interpretation of primary skin aetiology.

DIAGNOSIS AND TREATMENT

Clinical examination of a patient with cholestatic pruritus may be completely normal. Jaundice is absent in the majority of patients and its presence usually suggests advanced stage of underlying liver disease or

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severe biliary obstruction. Figure 1 shows a suggested approach to the assessment and management of cholestatic pruritus by GPs.

Cholestatic biochemistry (raised serum ALP), especially in female patients, should prompt checking of the liver autoimmune profile (particularly AMA) and serum immunoglobulins. In all cases of suspected cholestatic pruritus it is essential to perform a transabdominal ultrasound scan to assess liver and biliary architecture to rule out biliary obstruction (obstructive cholestasis). Presence of intrahepatic duct dilatation on ultrasound usually suggests biliary obstruction and, as such, the patient should be referred to secondary care (gastroenterology, hepatology, or surgery) for further investigations (computed tomography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography) as well as treatment (management usually involves endoscopy and/or interventional radiology and/or surgery depending on the aetiology and level of biliary obstruction). If malignancy is suspected (for example, unexplained weight loss) to be the cause of biliary obstruction patients should be referred on an urgent 2-week-wait (2WW) referral pathway.

Empirical treatment with guideline recommended antipruritic medications should be started early while appropriate investigations and referrals are being arranged. This is mainly because cholestatic itch rarely improves spontaneously and if left untreated it may become persistent and severe and could impact on sleep and mood, contributing to anxiety, depression, fatigue, and impaired quality of life. Contrary to common practice among clinicians, antihistamines (such as chlorpheniramine, cetirizine, loratadine, fexofenadine, and hydroxyzine) have not been shown to be effective in cholestatic pruritus.⁵ Antihistamines worsen fatigue and sicca symptoms (dry mouth and dry eyes) of PBC. However, due to their sedative properties some antihistamines may temporarily alleviate pruritus by inducing sleep. The use of moisturisers, emollients, and other topical preparations has not been submitted to studies in patients with the pruritus of cholestasis; however, their use should be encouraged to keep skin healthy.³ Our standard practice is to encourage all patients with pruritus to use topical application of aqueous cream with 1% menthol (for its coolant effect). This treatment may suffice in patients with mild and localised itch.

For moderate to severe, or generalised itch guideline recommended first-line therapy is with oral cholestyramine (cholestyramine,

Questran® Bristol-Myers Squibb). It is a non-absorbable anion exchange resin which is thought to act by removing potential pruritogens (bile salts) from the enterohepatic circulation by binding with them and enhancing faecal excretion. It is licenced for use in cholestatic pruritus. Although it is generally well tolerated, its unpleasant taste affects adherence (which may be improved by mixing with fruit juice). Adverse effects can include anorexia, constipation, diarrhoea, abdominal discomfort, or bloating. Colesevelam, a novel resin, is generally better tolerated and although evidence of its efficacy in cholestatic pruritus is equivocal, it should be offered to those who benefit from colestyramine but are intolerant to its taste or side effects. Use of both colestyramine and colesevelam in primary care is safe and does not need monitoring. In a retrospective review of 92 patients with PBC and itch treated between 2007 and 2011 at our centre in Newcastle, 61% of patients treated with colestyramine (mean dose 8 g/day, median duration 24 weeks) had complete or partial resolution of their itch. There are no data on the use of topical treatments or colesevelam at the centre.

Rifampicin (150–600 mg/day) and naltrexone (up to 50 mg/day), given orally are the guideline recommended second- and third-line drugs for those unresponsive to colestyramine/colesevelam. In our experience complete or partial resolution of itch can be achieved with rifampicin in up to 80% of patients, and with naltrexone in up to 50% of patients. These results are consistent with published studies and meta-analyses of rifampicin and opiate antagonists in cholestatic pruritus.⁶ However due to their side-effect profile, rifampicin and naltrexone need regular monitoring and should ideally be initiated in secondary care. Serious side effects associated with rifampicin include hepatitis, haemolytic anaemia, thrombocytopenia, and renal impairment. Rifampicin-induced hepatotoxicity is of serious concern and it is most likely to occur in the first 2 months of starting therapy. Therefore close monitoring of LFT every fortnight in the first 2 months of therapy, and at least once monthly thereafter is strongly recommended. Although uncommon, hepatitis can also be associated with naltrexone, therefore regular monitoring of LFT is recommended. Long-term use of both rifampicin and naltrexone is safe and effective in treating cholestatic itch and monitoring of blood tests can be done in primary care. In patients developing abnormal LFT, treatment should be immediately discontinued and referred to secondary care.

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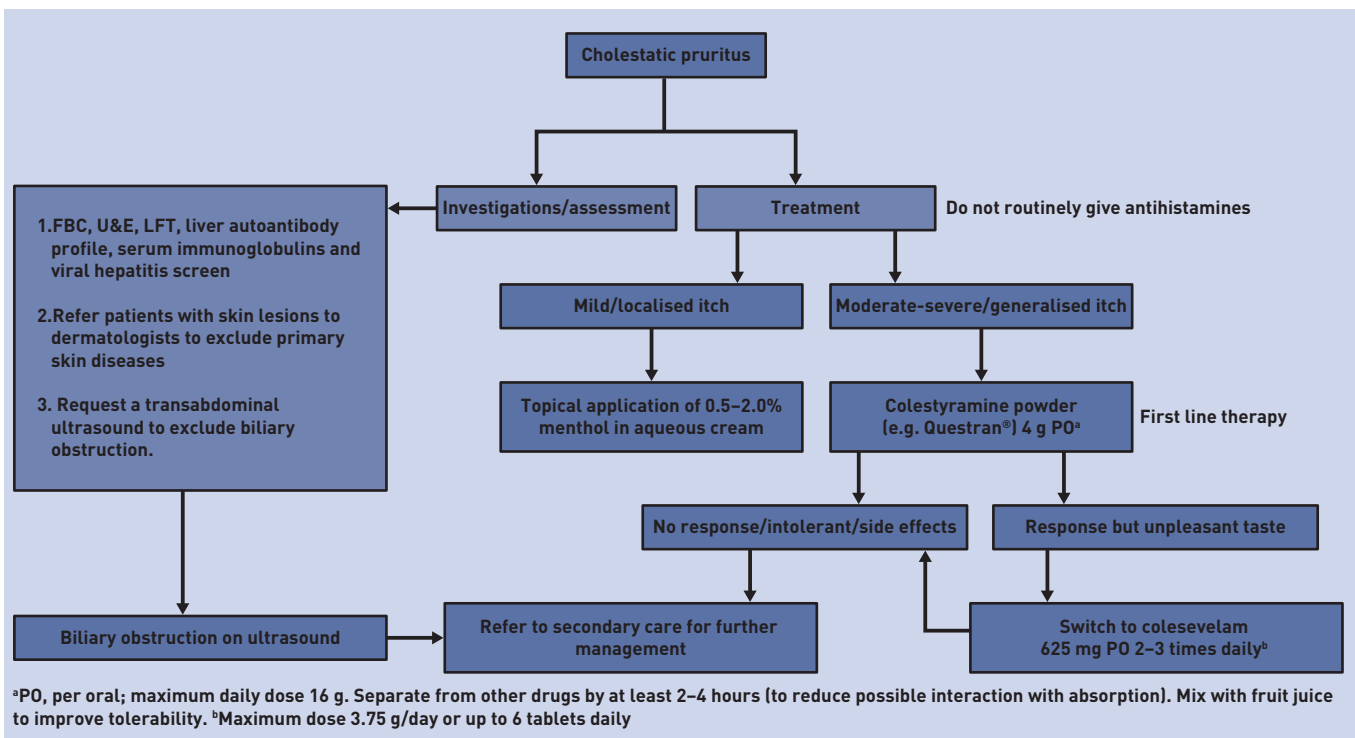


Figure 1. A suggested approach to management of cholestatic pruritus in primary care.