Cholestasis

What is cholestasis?[1]

Bile is a primary hepatocyte secretion. It is produced continuously but between meals it is stored in the gallbladder. About 0.5 litres of bile enters the duodenum each day.

Cholestasis is defined as: "*Stagnation, or a marked reduction, in bile secretion and flow. Cholestasis can be due to a functional impairment of the hepatocytes in the secretion of bile 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*[2] ."

There are several clinically important sequelae which contribute to the clinical presentation:

- Retention of conjugated bilirubin and its regurgitation into serum.
- Increased serum concentration of unconjugated bilirubin.
- Increased bile salts.

Conditions giving rise to cholestasis broadly fall into two categories:

- Those where there is a mechanical blockage in the duct system - obstructive or extrahepatic cholestasis[3] .
- Those where there are disturbances in bile formation - hepatocellular or intrahepatic cholestasis[4] .

The term obstructive jaundice is usually used to describe extrahepatic cholestasis. See list of associated diseases for conditions giving rise to cholestasis and follow links to find out more about them.

See the separate Jaundice article.

Who gets cholestasis? (Epidemiology)[5]

- This generally relates to the epidemiology of underlying conditions. Extrahepatic cholestasis accounts for 70% of all cholestasis cases.
- When looking at it as a whole, women are more affected due to the condition of cholestasis in pregnancy. See the separate Obstetric Cholestasis article. Biliary atresia and drug-induced cholestasis are also more commonly seen in women.
- Newborns and infants are more susceptible and more likely to develop cholestasis as a consequence of immaturity of the liver.

Cholestasis symptoms

History

When faced with patients who may have cholestasis, enquire about the following[5] :

- Jaundice - arises as a consequence of elevated serum conjugated bilirubin[6] . Ask about duration if known.
- Pale stools and dark urine - pale stools occur as no bilirubin reaches the gastrointestinal tract and dark urine results from reflux of conjugated bilirubin into blood which is excreted in the urine. Both of these features suggest cholestasis.
- Abdominal pain.
- Fever - suggests infection or cholecystitis.

- Pruritus - manifest by scratch marks (excoriation). This is a common but not universal feature (ranging from absent to severely disabling), the exact pathophysiology of which is not clearly understood [7] . There may be secondary skin infections if scratching is severe and, in children, there may be associated poor sleep, attention deficits, poor school performance and a form of hyperkinesis that may have importance regarding energy balance.
  NB: the ability to scratch oneself is something that develops over the first 14 months of life and therefore the very young baby may well experience the pruritus of cholestasis but be unable to do anything about it. These children invariably go on to scratch themselves as their abilities develop, starting at around 6 or 7 months of age. In the interim, the baby may be miserable, irritable and poor at socialising.
- Children - may have the above but also failure to thrive (due to malabsorption, anorexia, poor nutrient use), evidence of hormonal disturbances and secondary tissue injury.
- Medication and travel - take a full travel and drug history, including the use of herbal remedies and over-the-counter preparations.

Examination [5]

Look for the following:

- Clubbing.
- Icterus - cutaneous jaundice is usually seen at serum concentrations of about 85.5 µmol/L but scleral icterus can be seen at concentrations as low as 34.2 µmol/L.
- Pyrexia - suggests infection or cholecystitis.
- Abdominal pain - especially at the right upper quadrant (RUQ).
- Hepatomegaly - if so, estimate the size, regularity and presence of tenderness.
- Splenomegaly - this suggests the development of portal hypertension.
- Palpable or tender gallbladder.

- Hypercholesterolaemia[1] . This is a feature in some types of cholestasis. Unless there is long-standing disease or previous cardiovascular disease, there may not be any clinical manifestations of this (particularly in children). Alternatively, xanthomas may be found - look particularly in the palmar creases, below the breast, on the neck and, in the young child, in the nappy area.

At this stage if the patient is acutely unwell (eg, superimposed infections, dehydration and/or acute kidney injury) then consider referral to hospital immediately for admission and further management. If the patient is not acutely unwell, it is appropriate to organise investigations and referral to the hepatologists as an outpatient.

The history and examination may give some clues as to the likelihood of cholestasis but this can only be confirmed on the basis of LFTs - these will classically show an elevated serum bilirubin in proportion to the duration of the cholestasis, markedly raised serum alkaline phosphatase to >3 times its normal upper limit and raised gamma-glutamyltransferase (gamma-GT), compared with the transaminases. However, note that the rates of bile formation and flow cannot actually be measured. Therefore, investigations centre on assessing the serum concentrations of substances released into the bile and imaging of structures involved in the secretion of the bile.

Investigating cholestasis[5] [2]

Laboratory and liver function tests

The serum concentrations of conjugated bilirubin and bile salts are the most commonly measured parameters. As these are retained to different extents in various cholestatic disorders, their relative levels go some way to helping with cholestasis diagnosis. The serum bilirubin will help monitor progress. Other findings will typically include:

- A high alkaline phosphatase and gamma-GT in virtually all obstructive diseases and many hepatocellular diseases. Serum transaminases will also be raised in obstructive cholestasis and, to a lesser extent, hepatocellular disease.
- Elevated aspartate transaminase (AST) and alanine aminotransferase (ALT) suggest a more hepatocellular picture.
- Serum albumin and globulin will change little in the acute phase but albumin will decrease and globulin increase in chronic disease.

- Hyperlipidaemia will also be noted in some types of cholestasis where the ability to break down and excrete cholesterol is impaired. There is a picture of hypercholesterolaemia with a normal or low high-density lipoprotein.
- U&E and creatinine - acute kidney injury may be present.
- A haematology screen may show anaemia (where there is malignancy) and a raised white cell count (infection - eg, ascending cholangitis). Cholestasis leads to abnormally shaped cells and there may be a deficiency of vitamin K. Reticulocytosis points to prehepatic jaundice and it is worth checking the prothrombin time.

Further investigations may include the following (some requested by the specialists):

- Other blood tests - eg, autoantibody screen, hepatitis screen, blood cultures.
- Endoscopic retrograde cholangiography (ERCP - no dilated ducts seen on ultrasound scan) and percutaneous transhepatic cholangiography (PTC - dilated ducts seen on ultrasound scan) will provide insight into the cause of the obstruction.
- Magnetic resonance cholangiopancreatography (MRCP) - this is non-invasive investigation which will provide information about the hepatobiliary and pancreatic systems.
- CT scanning may provide some useful information and can complement ultrasonography, particularly in obese individuals where the latter may be challenging.
- Liver biopsy is the single most useful test but it carries risks and many diagnoses can be made before a biopsy is considered.
- Where tumours are found, CXR ± CT will be needed to look for evidence of spread or the primary focus.

Initial imaging

Initial imaging should include ultrasonography to identify obstructive liver disease; depending on the result, further investigation may be appropriate.

Note that patients who are acutely unwell - eg, jaundice, abdominal pain and fever - may have an abdominal X-ray, looking for aerobilia or localised ileus.

If the blood tests confirm cholestasis then these should be reviewed along with the presenting features, to determine a differential diagnosis, which might include the following.

Causes of cholestasis

Generally, the differential diagnosis of cholestasis in neonates and infants is much broader than in older children and adults because the immature liver is relatively sensitive to injury and its response is more limited. For example, in infants cholestasis may arise as a result of Gram-negative sepsis, heart failure, metabolic disease or exposure to minimally toxic substances. It is therefore prudent to search beyond the liver for a cause in these patients.

Obstructive cholestasis [3]

This is usually as a result of a physical obstruction; the most common causes are gallstones and carcinoma of the head of the pancreas. However, paucity of the ducts (eg, very small bile ducts such as in Alagille's syndrome - an autosomal dominant disorder associated with abnormalities of the liver, heart, skeleton, eye, and kidneys and a characteristic facial appearance) may lead to a functional obstruction [8] . Causes of cholestasis can be subdivided into:

- Obstruction of the lumen of the bile duct, such as gallstones, parasitic (eg, hydatid disease or roundworms) or iatrogenic (eg, post-cholangiography).
- Obstruction within the wall of the bile duct - sclerosing cholangitis, other types of cholangitis (eg, infectious cholangitis or associated with Langerhans' cell histiocytosis), cholangiocarcinoma, traumatic stricture and congenital stricture (eg, biliary atresia, choledochal cysts).
- Obstruction outside the bile duct, pressing into it, such as carcinoma of the head of the pancreas or of the ampulla of Vater, pancreatitis, porta hepatis tumours and chronic duodenal ulceration.

Hepatocellular cholestasis

The most common causes are cirrhosis and drug reactions (eg, phenothiazines, chlorpromazine, erythromycin, gold salts, anabolic steroids) but other causes include:

- Sclerosing cholangitis.
- Viral or alcoholic hepatitis.
- Septicaemia.
- Primary biliary cirrhosis.
- Alpha-1-antitrypsin deficiency.
- Inborn errors of bile acid synthesis.
- Total parenteral nutrition (TPN)-associated cholestasis[9] .
- There are more uncommon causes of hepatocellular cholestasis, including Dubin-Johnson syndrome, sickle cell disease[10] , benign recurrent intrahepatic cholestasis, Hodgkin's disease: mechanism unknown, inspissated bile in cystic fibrosis, erythropoietic protoporphyria - may cause precipitation of protoporphyrins in canalicular ducts, progressive familial intrahepatic cholestasis and Caroli's disease. Benign intrahepatic cholestasis of pregnancy[4] falls into this category.

Differential diagnosis[5]

Jaundice not due to cholestasis

- Unconjugated hyperbilirubinaemia.
- Dubin-Johnson syndrome.
- Rotor's syndrome.
- Carotenaemia.

Dark urine not due to bilirubinuria

- Haematuria.
- Drug ingestion.
- Dehydration.

Pruritus not due to cholestasis

- Atopic disease.
- Drug ingestion.
- Behavioural disorder.

Cholestasis treatment and management

Resuscitation and stabilisation of the acutely unwell patient should be the first priority if relevant.

Following this, management depends on the underlying problem. Cholestasis *per se* is not responsive to medical treatment[5] . The underlying cause has to be sought and addressed. Similarly, it is worth noting that some of the secondary effects of cholestasis that would usually be managed successfully with conventional treatment are not responsive and only resolve with treatment of the underlying cause of cholestasis. This includes:

- The pruritus of cholestasis which is not mediated by histamines and therefore antihistamines will be ineffective. European Association for the Study of the Liver (EASL) guidelines suggest the following[11] :
    - Bile sequestrants.
    - Rifampicin.
    - Oral opiate antagonists (naltrexone and nalmefene) are used as third-line therapy as they can reduce the sensation of itching.
    - Selective serotonin reuptake inhibitors (eg, sertraline) and gabapentin are used empirically in the management of cholestatic itch, typically in patients with pruritus unresponsive to other agents.
- The asthma-type picture which sometimes emerges in these patients.

- Hypercholesterolaemia - dietary measures will do little positive and may be counterproductive, particularly in children where cholestasis may give rise to secondary malnutrition. These patients have complex dietary needs, especially where the disease is long-standing and particularly in the paediatric population. Whilst the fat intake needs to be reduced, the protein and calorie intake needs to be maintained. There may also be problems in the assimilation of fat-soluble vitamins (A, D, E, K). It is advisable to involve a dietician at an early stage.

- Osteopenia should be excluded in patients with chronic cholestasis (see 'Complications', below) [12] . If this is present, bisphosphonates are the drugs of choice.

Editor's note

Dr Sarah Jarvis, 28th February 2022

Odevixibat for progressive familial intrahepatic cholestasis

Results from clinical trials suggest that, in people with progressive familial intrahepatic cholestasis (PFIC) types 1 and 2, odevixibat reduces bile acid levels in the blood and pruritus compared with placebo. There are limited data for other types of PFIC.

The National Institute for Health and Care Excellence (NICE) has reviewed the evidence above [13] . The committee also took into account the invasive nature of other treatments, the young age at which PFIC can develop and the benefits from delaying or stopping lifelong immunosuppression after a liver transplant.

NICE therefore advises that odevixibat is recommended, within its marketing authorisation, as an option for treating progressive familial intrahepatic cholestasis (PFIC) in people aged 6 months and older. However, it is recommended only if the company provides odevixibat according to the commercial arrangement.

Cholestasis complications

- Retention of biliary salts results in injury to cellular membranes throughout the body but hepatocytes are most affected (and therefore the problem is exacerbated). Thus, cholestasis can give rise to secondary liver conditions such as hepatic fibrosis.

- A well-described peripheral complication of chronic cholestasis is metabolic bone disease (osteopenia, osteoporosis and occasionally osteomalacia) - sometimes referred to as hepatic osteodystrophy [12] .
- Bleeding tendencies - particularly nosebleeds (which may be life-threatening) - affect the paediatric patient group [14] .
- Individuals with chronic cholestasis may develop an asthma-type wheeze which is not responsive to conventional asthma therapy and which disappears with treatment of the cholestasis [15] .
- There may be complications from investigative procedures (eg, cholangitis post-ERCP, bleeding post-biopsy).

Further reading

- British Liver Trust
- Children's Liver Disease Foundation
- Kapoor BS, Mauri G, Lorenz JM; Management of Biliary Strictures: State-of-the-Art Review. Radiology. 2018 Dec;289(3):590-603. doi: 10.1148/radiol.2018172424. Epub 2018 Oct 23.
- Palmer M, Regev A, Lindor K, et al; Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease. Aliment Pharmacol Ther. 2020 Jan;51(1):90-109. doi: 10.1111/apt.15579. Epub 2019 Nov 25.

Last updated by: Dr Hayley Willacy, FRCGP 29/12/2021	
Peer reviewed by: Dr Colin Tidy, MRCGP 29/12/2021	**Next review date:** 28/12/2026

View this article online at: patient.info/doctor/cholestasis

Discuss Cholestasis and find more trusted resources at Patient.