Diagnosis and Management of Cholestatic Liver Disease

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Cholestasis (slowing of bile flow) may be acute or chronic and affect any age group. In infants and children the causes are congenital or inherited and as a result of improved management some affected children now survive to adulthood. Although jaundice is a hallmark of cholestasis it may be absent, particularly in adults with chronic cholestatic liver disease most of whom are entirely asymptomatic. A detailed history and physical are crucial to the diagnosis and noninvasive radiologic tests (ultrasound, computerized tomography scan, and magnetic resonance cholangiography) greatly facilitate diagnosis, particularly when the cause is extrahepatic. Only if sufficient portal tracts (>10) are present on liver biopsy examination can this test reliably evaluate damage to the small bile ducts. Therapy should address both the cause and the consequences of retained bile acids within the liver, and diminished delivery of bile to the gastrointestinal tract. Therapies should address symptoms, mostly pruritus and prevention, particularly osteoporosis and osteomalacia. Portal hypertension can be an early event in chronic cholestatic liver disease, sometimes occurring before the development of cirrhosis. Ursodeoxycholic acid improves the biochemical markers of cholestasis regardless of cause and may delay liver disease progression; only liver transplant is potentially curative.

The term cholestasis is Greek in origin, meaning bile stoppage. In its most overt form, cholestasis presents to the clinician as jaundice. However, jaundice is only the tip of the iceberg of cholestatic liver disease. The introduction of screening blood work has allowed us to appreciate that much chronic cholestatic liver disease is anicteric. If symptoms are present, generalized pruritus without a skin rash predominates. Those with no symptoms generally are identified at a time when routine laboratory tests are being performed or during a work-up for another disease when an increase is noted in the level of serum alkaline phosphatase and/or γ-glutamyltranspeptidase (GGT). The early stages of a cholangiopathy caused by, for instance, primary biliary cirrhosis (PBC), may be identified on liver histology in individuals who have entirely normal serum biochemical tests but who test positive for antimitochondrial antibodies (AMA). Thus, the scope of cholestatic liver disease is much greater than one would at first appreciate.

Approach to Cholestasis

The first approach is always the history, which often is very pertinent in both acute and chronic cholestasis. Jaundice is confined predominantly to those with acute or acute-on-chronic cholestasis because end-stage chronic disease rarely is seen because liver transplant supervenes. A thorough drug history is imperative. Any medications taken within 6 weeks of presentation may be incriminated and only one dose may be sufficient to initiate disease, but a 1-time medication often is forgotten (eg, a benzodiazepine borrowed from a friend to facilitate sleep on a red-eye airplane ride). It may be impossible to identify the specific agent, such as in a herbal remedy mixture. The liver biopsy specimen in Figure 1 was from a woman whose jaundice resolved once it was realized she was drinking a new herbal tea. Few women consider oral contraceptives a medication, and although they rarely by themselves induce clinical manifestations of cholestasis, except in those who are heterozygotes for MDR3 deficiency, they not infrequently tip the balance from an acute anicteric hepatitic condition to a severely pruritic, acute cholestatic hepatitis (eg, in a teenager with infectious mononucleosis). MDR3 is the phosphatidylocholine translocator across the hepatocyte canalicular membrane. Similarly, a young man wanting to build up his muscle bulk may deny any over-the-counter muscle builders—those containing androgen-like substances may cause cholestasis. Probably the most common in-hospital/intensive care unit consultation request for jaundice is in the postoperative patient who is on TPN and is septic; in this situation it is hard to know whether it is the TPN and/or the sepsis that is causing the cholestasis. Cholestasis secondary to either TPN or sepsis may be prolonged and, albeit rare, may lead to progressive liver disease.

If the surgery has been in the region of the biliary system, inadvertent damage to the bile duct also needs to be considered. Having exhausted the personal history, the family history also is very pertinent. Jacquemin et al, a French pediatrician, noted that there were many women in the family of a young child with progressive familial intrahepatic cholestasis (type 3) who had suffered from intrahepatic cholestasis of pregnancy (ICP). Genetic testing subsequently revealed that the heterozygote state of the MDR3 mutation responsible for PFIC type 3 may be associated with a number of cholestatic conditions that include ICP, intraductal cholesterol gallstones, and, as previously mentioned, the propensity to develop jaundice after estrogen therapy. Another astute clinician traced back 2 prior

Abbreviations used in this paper: AMA, antimitochondrial antibodies; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane regulator; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyltranspeptidase; ICP, intrahepatic cholestasis of pregnancy; MDR3, human multidrug resistance gene-3; MRCP, magnetic resonance cholangiopancreatography; MRP, multidrug resistance proteins; PBC, primary biliary cirrhosis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.
generations of a young man with idiopathic ductopenia and found several family members with biliary cirrhosis and/or hepatic tumors. However, to date, no specific genetic mutation for this form of adult-onset ductopenia has been described. These clinical observations serve to remind us of the great value of thorough history taking.

The physical signs of cholestasis are most evident in young children in whom the cholestasis often is congenital and severe. Now that transplantation has become so successful for most of these inherited causes of cholestasis, the grossly disfiguring, long-term physical effects (eg, generalized tuberous xanthomata and green teeth) rarely are seen (Figures 2 and 3). The most obvious physical signs of cholestasis are scratch marks and shiny nails secondary to persistent scratching. Chronic cholestasis eventually leads to increased skin pigmentation. Xanthelasmas, a common feature of PBC in the past, now is seen less often.

Typically, the biochemical markers of chronic cholestasis are an increase in the levels of the bile duct enzymes alkaline phosphatase and/or GGT. Although the serum alkaline phosphatase level may be increased in bone disease, gastrointestinal disease, or during pregnancy, the GGT level is almost specific to the liver. Increased serum levels of these enzymes likely are caused by the damaging effect of high concentrations of bile acids on intracellular and biliary membranes. The measurement of fasting serum bile acids is the most sensitive test for cholestasis, but this test is not generally available. In the early phase of cholestasis, observed particularly well during intrahepatic cholestasis of pregnancy, the serum aminotransferase levels are more likely than the alkaline phosphatase level to be increased.

The serum bilirubin level in its conjugated form may or may not be increased in cholestasis. Gilbert syndrome, which gives rise to an unconjugated hyperbilirubinemia, affects 7% of the adult population and accentuates the hyperbilirubinemia of any underlying liver disease and thus may confuse the picture if the bilirubin is not fractionated. An infiltrative disorder of the liver may be associated with a very similar biochemical pattern to that of cholestasis (eg, amyloidosis, fatty liver, and lymphoma). Sometimes serum levels of aminotransferases may be very high (>1000 IU/L) and fluctuate despite obvious cholestasis—this pattern is typical of biliary obstruction caused by intraductal stones. An isolated increase in the serum GGT level may be owing to enzyme induction alone such as after alcohol consumption or in those who need to take anti-epileptics or other drugs that act as enzyme inducers.

Further Investigations in Cholestasis

Ultrasonography revolutionized the diagnostic work-up of apparent cholestasis because it could clearly distinguish intrahepatic vs extrahepatic biliary tract disease. However, although ultrasound is an excellent technique, it is very technician- and interpreter-dependent, whereas computerized tomography scan is less technician-dependent. For this reason, computerized tomography is frequently the test of first choice, even though it is not as good as ultrasonography at delineating the biliary tree.

If the bile ducts are not dilated in an individual whose history suggests an extrahepatic cause for their cholestasis, clinical judgment should be pursued and another procedure or repeat ultrasound should be performed within the next 2 weeks. This may be seen with very early pancreatic carcinoma or an ampullary carcinoma. In patients who have just passed a common duct stone there nearly always will be stones remaining in the gall bladder, even though the duct system is no longer dilated.
Extrahepatic biliary obstruction may be caused by stones, tumors, cysts, parasites, or stricture(s) of the biliary tree. Further work-up of dilated ducts depends on the presumed cause. If in doubt as to whether a therapeutic maneuver will solve the problem, it is probably wise to perform magnetic resonance cholangiography next, if only to avoid an invasive procedure that may not be needed, for example, in a patient with anicteric primary sclerosing cholangitis (PSC).

**Visualization of the Bile Ducts: Endoscopic Retrograde Cholangiopancreatography Versus Magnetic Resonance Cholangiopancreatography**

The gold standard for visualizing the extrahepatic biliary system is endoscopic retrograde cholangiography, but even in good hands it carries a significant complication rate. Around 3%-5% will develop some degree of pancreatitis. In individuals in whom the need for a therapeutic maneuver is not anticipated, magnetic resonance cholangiopancreatography (MRCP) is the safer option. The sensitivity and specificity of MRCP compared with endoscopic retrograde cholangiopancreatography (ERCP) has been best evaluated in patients with PSC. Although many would argue about which is the best test to delineate the second- and third-generation intrahepatic bile ducts, few would argue that ERCP gives a clearer picture of the pancreatic portion of the biliary tree. The negative predictive value for MRCP is 94%, and the positive predictive value ranges between 85% and 94% when compared with ERCP.

One situation in which it is far safer to use MRCP than ERCP to delineate the biliary tree is when a portal biliopathy (which may look very similar to PSC) secondary to portal vein thrombosis is present. Intraductal stones also may be seen and these patients not infrequently present with cholangitis. Septic cholangitis with multiple liver abscesses also may be confused with PSC, but the changes resolve completely after appropriate antibiotic therapy. Similarly, viral or parasitic cholangitis, formally a common feature of late-stage acquired immune deficiency syndrome, can look like PSC. The biliary tree may return to normal if successful eradication of the causative infection can be achieved. Now rare in North America, acquired immune deficiency syndrome cholangiopathy remains common in the developing world where a clinical diagnosis is generally all that is available. Autoimmune pancreatitis also is associated with a picture that may be confused radiologically with PSC, although it particularly affects the lower end of the common bile duct—this too may resolve with corticosteroids.

**Intrahepatic Cholestasis**

**Physiology and Pathophysiology**

Both inherited and acquired liver diseases may cause intrahepatic cholestasis. It is the identification of the many genetic causes so prevalent in the pediatric population that has facilitated our understanding of intrahepatic bile flow. Intrahepatic cholestasis may be caused by disease at the subcellular level or be caused by abnormalities of canalicular transport or motility or from damage to small biliary ductules. Cloning of the canalicular transporters in the early 1990s identified several different mutations that now have been shown to be responsible for many of the inherited cholestatic syndromes of childhood. Antibodies now are available that allow visualization of the distribution of these transporters in liver tissue by using immunohistochemistry (Figure 4).

Bile acids synthesized from cholesterol within hepatocytes are transported across the cell in vesicles and shunted along microtubules to the canalicular membrane. Thus, any hepatic injury that damages these intracellular organelles will promote cholestasis—alcohol is the most common of such toxins. At the canalicular membrane bile salts predominate are transported across the canalculus by the bile salt excretory pump, whereas the phosphotidylcholine necessary for biliary micelle formation is flipped across the canalicular membrane by the MDR3 transporter. Bilirubin and organic anions predominantly are transported by the membrane transporter MRP2, and cholesterol uses yet other transporters to gain access to the bile.

There are other mechanisms that if interrupted may cause cholestasis at the level of the canalculus. The canalculus, a tube with a closed end, requires a mechanism that propels its luminal contents distally. This is achieved by intermittent contraction of actin-myosin strands that surround each canalculus. Paralysis of this actin-myosin network causes marked dilation of canaliculi, described by hepatopathologists as biliary cholestasis (Figure 5). Recently studies have identified the absence of villin protein in the liver of some children with gross canalicular abnormalities. The lipid content of the canalicular membrane if altered will change its motility and can cause biliary cholestasis (eg, with estrogens). If the tight junctions that bind the 2 opposing canalicular membranes of adjacent hepatocytes are not held in close apposition, this will allow leakage of canalicular contents back into the sinusoid. A missense mutation of the tight junction protein causes just this. However, far less rare causes of leaky tight junctions are distal obstruction and/or ductopenia. Both in children but particularly in adults, the myriad of causes of ductopenia are the most common causes of chronic intrahepatic cholestasis in general gastroenterologic practice.
form micelles. Hydrophobic bile acids destroy biliary membranes if not embedded in micelles. Subsequent crystallization of cholesterol and the formation of tiny stones in the canaliculus cause considerable hepatocyte damage, requiring the need for liver transplantation.20

Other genetic defects may be responsible for damage to the interlobular bile ducts, causing hypoplastic ducts. Alagille syndrome21 is caused by a mutation in the JAG1 gene.22 This is an autosomal-dominant condition that affects many structures (eg, bile ducts, heart, face, skeleton, kidney, and eye). The gene is a ligand for the notch-family receptor. The notch signaling pathway is very important in development. Clinical presentation of this disease varies greatly and sometimes it may not even be recognized until early adulthood, although most often affected children are jaundiced as babies and are noticed to have a prominent forehead, a pointed chin, low-set ears, and hypertelorism.

Children with cystic fibrosis caused by mutation of the CFTR gene (the gene product is located on all epithelial cells, thus biliary epithelial cells are involved) now are managed so successfully in terms of their lung disease that the biliary complications of this very common inherited disease are prominent in individuals surviving into adulthood. In cystic fibrosis the bile ducts become plugged with viscous material that initiates an inflammatory condition of the intrahepatic bile ducts leading to focal biliary cirrhosis.23

Many of the intrahepatic conditions that cause cholestasis in adults (described later) also may affect children, the most common being PSC, which in children frequently overlaps with autoimmune hepatitis.24,25

### Cholestasis in Adults

Prescription drugs, over-the-counter drugs, and herbal remedies are the most common causes of acute cholestasis in adults, which may sometimes progress to a chronic vanishing bile duct syndrome.26 Thus, drugs may induce cholestasis at the subcellular, the canalicular, or the ductal level.

ICP is also a very heterogeneous condition, therefore different biochemical patterns may be observed. It has long been recognized that there is a genetic component to ICP because the disease is much more common in Chile and in Scandinavia. Nevertheless, because the incidence of this third-trimester complication of pregnancy is diminishing, there also must be external factors that influence its clinical presentation. The biochemical abnormalities seen in ICP are predominantly high serum transaminase levels, and the GGT levels may or may not be increased. However, very high levels of bile acids are present in all cases.8 The condition responds dramatically to treatment with ursodeoxycholic acid by alleviating the pruritus in the mother and reducing the chance of prematurity or stillbirth of the fetus.27

In adults, the vanishing bile duct syndrome is the most common cause of chronic intrahepatic cholestasis (Table 1). The diagnosis can be made only by liver biopsy examination and at least 10 portal tracts need to be present, with at least half of them with absent ducts, before a confident diagnosis of vanishing bile duct syndrome can be made.28 Inherited causes of vanishing bile duct syndrome already have been discussed. Acquired causes include immune-mediated, infectious, malignant, vascular, toxic (including drug-induced), and idiopathic. The most common are immune-mediated, such as PBC, PSC,
sarcoïdosis, graft-versus-host disease, and allograft rejection. The diagnostic hallmark for PBC, namely the AMA, facilitates recognition of this disease. But there is an entity simply called AMA-negative PBC,29 such cases in all other ways resemble AMA-positive PBC.29 Only in those who test negative for AMA is it necessary to show a normal biliary tree via MRCP (or ERCP), to be sure the individual does not have PSC. A beaded appearance caused by stricturing and dilation of the extrahepatic and/or intrahepatic biliary system is the typical pattern of PSC,30 but there are individuals who manifest cholestasis for many years (even with concomitant inflammatory bowel disease) who remain with a radiologically normal hepatic biliary tree for a long time before overt PSC is seen. Sometimes liver biopsy examination will show typical lesions with onion-skin fibrosis of the small intralobular bile ducts despite normal large ducts. Such cases have been described as having small-duct PSC.31

If fibrotic duct lesions typical of PSC are not seen, yet there is a cholangiopathy visible on liver histology despite normal cholangiographic appearances of the larger ducts and AMA are undetectable, this poses a diagnostic dilemma. Fortunately, such unknown cholangiopathies are rare. An overlap of autoimmune hepatitis and PSC is particularly common in children,24,25 but may affect adults.32 There is no evidence to suggest that the outcome of such overlap syndromes is any different from typical PSC,33 but survival is certainly worse than that of typical autoimmune hepatitis.

### Table 1. Causes of Vanishing Bile Duct Syndrome (Ductopenia)

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Congenital</td>
<td>Alagille syndrome (and nonsyndromatic)</td>
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<td></td>
<td>Cystic fibrosis</td>
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<td></td>
<td>Duct plate abnormalities</td>
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<td>PFIC-3</td>
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<td>Infectious</td>
<td>Cytomegalovirus</td>
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<td></td>
<td>Biliary sepsis</td>
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<td>Parasites</td>
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<td>Idiopathic</td>
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<td>Malignant</td>
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<td>Cholangiocarcinoma</td>
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<td>Mastocytosis</td>
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<td>HA thrombosis</td>
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<td>PNH</td>
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<td></td>
<td>Portal biliopathy</td>
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<td></td>
<td>Vasculitis (PAN)</td>
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<td></td>
<td>Henoch-Schönlein (surgical-localized)</td>
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<tr>
<td>Toxic</td>
<td>Drugs (after cholestatic hepatitis)</td>
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<td></td>
<td>Formaldehyde</td>
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<td></td>
<td>Fluorouridine</td>
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<td>Immune</td>
<td>PBC</td>
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<td>PSC</td>
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<td>Sarcoïd</td>
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<td>Graft vs host disease</td>
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<td>Allograft rejection</td>
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<td></td>
<td>Overlap autoimmune hepatitis/PSC</td>
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### Consequences of Cholestasis and Its Treatment

Treatment both of the consequences of the retention of hydrophobic bile acids within the liver and the effects of diminished quantities of bile acid reaching the bowel is necessary. The retention of bile acids within the hepatocyte has a detergent effect on the intracellular membranes and promotes hepatocyte apoptosis and hepatic fibrosis. Retention of the biliary lipids normally excreted in bile causes hypercholesterolemia and xanthoma. Pruritus is the most frequent complication of bile retention, but the exact cause of pruritus in cholestasis is much debated.

The reduced micellar concentration of intraluminal bile acids that results from stagnant bile flow causes steatorrhoea and weight loss as well as vitamins A, D, E, and K deficiency. The consequences of diminished bile acids within the bowel are most pronounced in children; nevertheless, the consequences in adults also may be severe.

### Symptomatic Treatment

The most prevalent symptom of cholestasis (even if anicteric) is pruritus, a symptom that often is underappreciated by physicians but when severe may cause marked sleep disturbance and sometimes cause the patient to even contemplate suicide. Thus pruritus should never be ignored. The first line of treatment is the anion-exchange resin, the best-known being cholestyramine. This agent often gives rise to gastrointestinal disturbance and is poorly tolerated by some but is effective in 80%. It needs to be taken appropriately (ie, before and after breakfast and 4 hours from any other oral medication) and taken on a daily basis to prevent pruritus, not just taken when pruritus is present. The second line of therapy is the antibiotic rifampin.34 This is effective in 50%; its mechanism of action remains unclear. The usual dose is 150 mg twice daily. Patients do need to be monitored for the albeit rare complications of hepatitis, hemolytic anemia, and renal dysfunction.35 As a third-line therapy, opioid antagonists, given in very low doses initially and gradually increasing the dose as the patient is able to tolerate the symptoms typical of withdrawal, is very effective but when used chronically may give rise to the chronic pain syndrome.36 Recently, treatment with the antidepressant Sertraline has been shown to be effective in some individuals with recalcitrant pruritus.37 Many notice an improvement in pruritus if they are in the sun (without sunblock). In acute severe cholestasis, for example, ICP with severe pruritus, apheresis, or perhaps even MARS, can be used with tremendous relief of symptoms.38 In those with chronic cholestasis and unrelenting pruritus, liver transplantation may be necessary but partial biliary diversion very effectively eliminates the pruritus of chronic cholestasis in children with PFIC39 who may have severe pruritus but no liver failure, and thus have no need for liver transplantation.

### Preventive Strategies

Osteomalacia and/or osteoporosis are associated with severe chronic cholestatic liver disease (eg, that caused by PBC and PSC). Osteomalacia is seen only when there is profound icteric cholestasis with inadequate calcium and vitamin D supplementation. Calcium supplementation also benefits those
with osteoporosis, with the addition of bisphosphonates when necessary. In individuals with chronic (even anicteric) cholestatic liver disease, screening for bone mineral density should be routine at diagnosis and every 1 or 2 years.

Portal hypertension in patients with biliary tract disease may occur before the development of cirrhosis, caused by nodular regenerative hyperplasia and thus the usual screening rules with regard to the platelet count do not apply to those with disease of the portal tracts.

Specific Therapies

Although many of the genetic mutations responsible for the several forms of congenital cholestatic liver disease have been described, gene therapy is still only a hope for the future. There are a few specific therapies for cholestatic liver disease, they include antibiotics for bacterial cholangitis and corticosteroids for autoimmune cholangitis. Nonspecific therapies that promote bile flow—namely hydrophilic bile acids (eg, ursodeoxycholic acid [UDCA]), make physiologic sense. UDCA leads to improved liver biochemistries, liver histology, and perhaps survival (in patients with PBC). The role of UDCA therapy in the management of PSC is uncertain. Although corticosteroid therapy may play a role in very early PBC, steroids given to individuals with more advanced cholestatic liver disease promote severe osteoporosis and must be avoided. In some children with PFIC3, UDCA may reduce damage to bile ducts. Only when UDCA is given to women with ICP does UDCA lead to a decrease in total serum bile acids and loss of pruritus.

When all strategies have failed and the liver is failing or the consequences of chronic cholestasis are refractory to treatment and intolerable (eg, pruritus), then liver transplantation is curative. Individuals given a liver transplant for chronic cholestatic liver disease have an excellent outcome.

References

primary sclerosing cholangitis have a favourable long term prognosis. Gut 2002;51:731–735.

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