CONSENSUS DOCUMENT RECOMMENDATIONS FOR MANAGEMENT OF LIVER AND BILIARY TRACT DISEASE IN CYSTIC FIBROSIS

I. INTRODUCTION

Although involvement of the liver and biliary tract has been recognized as a complication of cystic fibrosis (CF) since Anderson's initial description of CF in 1938[1], the clinical significance of hepatobiliary disease in CF had not been well characterized until recently. The clinically silent development of liver complications has often been eclipsed by the obvious manifestations of pulmonary and pancreatic abnormalities. Because of improved life expectancy for individuals with CF now reported as 31 years, liver disease has assumed greater importance to CF patients and their caretakers. Unfortunately, clinical identification of liver disease in CF has been difficult and inaccurate because of the general lack of symptoms when the fibrotic liver lesion is developing. Thus, early diagnosis and therapeutic intervention have not been possible. In recent years, advances in our understanding of the function of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein in bile duct epithelia, and of the mechanisms of fibrogenesis in the liver, have provided a stronger scientific basis for the pathogenesis of disease. This had led to insights concerning novel therapeutic approaches. For these reasons, the Cystic Fibrosis Foundation has recognized the need to revise the previous *Recommendations For Management Of Liver And Biliary Tract Disease In Cystic Fibrosis*, published in 1989, to reflect the new scientific advances and related clinical information. For this purpose, the Cystic Fibrosis Foundation assembled a committee of experts to develop new recommendations. This document is the consensus of that group.

II. BASIC DEFECT IN BILIARY EPITHELIUM

The expression of the CFTR gene in the normal human liver is in the epithelia of the intrahepatic and extrahepatic bile ducts and the gallbladder; the CFTR protein is localized to the apical domain of these cells[2]. CFTR is not expressed in other cells of the liver, including hepatocytes[2]. It is therefore likely that CFTR is involved in chloride and water secretion into bile at the ductal level[3]. Research has shown that CFTR gene mutations cause reduced, dysfunctional or absent c-AMP-inducible chloride channel function in bile duct epithelia[3]; thus, impaired or abolished CFTR-induced chloride efflux across these cells appears to result in concomitant reduction in water and sodium movement into bile. It is also possible that CFTR regulates other ion channels in bile duct epithelia. The relative importance of CFTR in relation to other chloride channels— to enhance bile flow and dilute biliary fluid— remains to be determined. However, CFTR mutations most certainly lead to abnormalities in the composition, consistency, alkalinity or flow of bile which, in turn, may contribute to the pathogenesis of the liver lesions observed in CF. Although specific gene mutations (genotypes) have been associated with the severity of pancreatic involvement in CF, there has been no demonstrated relationship between CFTR mutation frequency or genotype and the presence of clinically detectable liver disease in CF patients[4,5,6]. However, there does appear to be a lower frequency of liver disease in pancreatic sufficient CF patients[7,8].

Because all CF patients are presumed to have abnormal CFTR in the biliary tree, it is unclear why all patients do not develop clinically significant liver disease. In fact, most CF patients do *not* develop clinical symptoms or signs of liver disease despite the probable presence (based on autopsy series) of focal biliary cirrhosis in the majority of older patients. This variable onset and severity of liver disease suggests that there are other modifying genetic or environmental factors that determine if hepatobiliary involvement will be of clinical significance. In this regard, Duthie et al.[9] found that the HLA haplotype B7-DR15-DQ6 was associated with an increased risk of chronic liver disease in male CF patients,

implicating a possible immune pathogenesis of hepatobiliary injury in addition to the CFTR defect. It should be pointed out that, as the median survival improves in CF, a longer period of time will be available for the progression of portal fibrosis and cirrhosis; thus, complications of liver disease and portal hypertension may become more common.

III. PATHOGENESIS OF HEPATOBILIARY INJURY IN CF

A spectrum of hepatobiliary manifestations is observed in CF (Table I). The most important clinically is the development of biliary obstruction and periportal fibrosis. The mechanism causing these liver lesions in CF has been attributed to focal inspissation of biliary secretions in intrahepatic bile ducts that gradually leads to the development of portal fibrosis, bridging and, eventually, to cirrhosis (Figure 1). Factors that contribute to the abnormal viscosity, decreased flow and increased concentration of components of bile in CF may be: (a) defective chloride transport, sodium reabsorption and bile dilution in intrahepatic bile ducts; (b) impaired secretion of mucins and other protective proteins from submucosal glands; or (c) increased glycine-conjugated bile acids. Altered bile composition or decreased bile flow presumably causes obstruction of small biliary ductules that may induce collagen deposition in portal tracts. For example, secondary hepatocyte injury (perhaps by hydrophobic bile acids) may release pro-inflammatory cytokines, growth factors, or lipid peroxide products that recruit and activate hepatic stellate cells (also called lipocytes, Ito cells, and fat-storing cells) to synthesize collagen[10]. Second, injury to bile duct epithelial cells[11] may cause these cells to release cytokines and growth factors that may directly induce collagen synthesis by stellate cells[12]. And third, inflammation caused by bile ductule obstruction and injury may recruit other cells (neutrophils, macrophages, lymphocytes) that generate cytokines responsible for the stellate cell recruitment and activation. This process begins focally in the liver, possibly because of interductal connections that may allow adequate bile drainage of some areas[13].

As the fibrogenic process proceeds, bridging fibrosis develops into multilobular cirrhosis, so-called because of the large regenerative nodules formed as a result of the initial focal process. *This progression from cholestasis (decreased bile flow) to focal biliary cirrhosis to multilobular cirrhosis takes years to decades and should be viewed as a continuum.* The contribution of apoptosis (programmed cell death) of the bile duct epithelia or hepatocytes to the liver lesions in CF has not been determined, although it has been suspected in other biliary diseases[14]. Although some reports claimed that extrahepatic stenosis of the common bile duct (as it courses through the pancreas) contributes commonly to the hepatic fibrosis in CF[15], subsequent reports indicate that this phenomenon is relatively rare[16,17].

Other liver lesions present in CF include neonatal cholestasis and hepatic steatosis. Neonatal cholestasis generally occurs in conjunction with complicated meconium ileus and the use of parenteral nutrition[18]; it is characterized by inspissated, eosinophilic secretions in portal tract bile ducts. Among patients who eventually develop cirrhosis, this lesion is rare[4], thus raising the question as to whether it is predictive of progressive liver disease. Hepatic steatosis in CF may be related to many factors including: malnutrition[19], essential fatty acid deficiency[20], other dietary factors[21], the effect of elevated blood levels of cytokines (e.g., tumor necrosis factor)[22], ethanol ingestion in older patients, or perhaps the genetic defect itself. Curiously, many cases of steatosis occur in the presence of excellent nutritional status. The relationship between steatosis and the development of fibrosis and cirrhosis in CF is undetermined; however, in other clinical scenarios, steatosis may progress to cirrhosis[23,24]. Hepatic congestion may result from right-sided congestive heart failure, not uncommon in older patients with CF. Over years, this lesion may progress to cirrhosis and liver failure. The pathogenesis of micro-gallbladder in CF is unknown; however, the high expression of CFTR in fetal gallbladder[25] suggests the possibility of a developmental abnormality.

IV. PREVALENCE OF HEPATIC AND BILIARY DISEASE

Because of the lack of sensitive diagnostic markers of liver involvement in CF, current prevalence rates should be considered estimates that most likely underestimate the true risk. Defining "clinically significant liver disease" in CF is problematic. Many patients with cirrhosis, caused by CF or a variety of other causes, will be well-compensated, completely

asymptomatic, and may even have normal liver blood tests. However, these patients are prone to slow or rapid decompensation caused by disease progression, viral infection, or other poorly defined factors. Decompensation includes development of gastrointestinal hemorrhage, ascites, fatigue, weight loss, anorexia, jaundice and pruritus, encephalopathy, and hypersplenism caused by disease progression, viral infection, or other poorly defined factors. Thus, current hepatology practice is the following: to identify patients with portal fibrosis, cirrhosis, or portal hypertension of any cause early in its course; to take measures to anticipate, prevent, and treat complications; and to educate the patient and family about symptoms, complications, and treatment of liver disease and portal hypertension, even if intervention is to be delayed. CF patients should be treated no differently. The presence of hepatic disease may also influence the choice and dosing of antibiotics and other medications.

The recent literature contains prevalence data from three sources, giving different prevalence estimates: voluntary reporting to the CF Foundation Patient Registry, Annual Data Report from U.S. CF centers[26], retrospective review of single and multiple center experience[27,28], and prospective evaluation (including imaging studies) for frequency of hepatobiliary abnormalities[15, 4]. Data reported on 19,064 patients to the CF Foundation Patient Registry, Annual Data Report in the U.S., in 1996, indicated a prevalence of hepatic cirrhosis (with portal hypertension) from a low of 0.1% in patients at 2 to 5 years of age, to a peak of 1.7% at 18-24 years of age, to 1.4% at 45+ years of age, for an overall prevalence rate of 1.0%[26]. Gallbladder disease requiring surgery was one-third as common as cirrhosis. Elevated serum liver enzymes were reported in 2.4% of patients and liver disease that required gastroenterology consultation was reported in 2.0% of patients. Hepatic disease was the primary cause of death in 1.6% of deaths, down from 3.4% of deaths in the 1995 registry data, but still remaining the second most common cause of death after pulmonary decompensation. Fourteen patients underwent liver transplantation in 1996, according to the CF Foundation Patient Registry, Annual Data Report.

Scott-Jupp et al.[28] retrospectively examined the records of 1100 CF patients from seven centers in England and found that 4.2% had clinical liver disease (defined as hepatomegaly, splenomegaly, or both). Elevated liver enzymes (AST, ALT, or GGT) were present in 12.9% of those examined. Clinically apparent biliary tract disease (defined as biliary colic plus gallstones on imaging studies) was present in 0.55% of patients. Clinically apparent liver disease peaked at ages 16-20 years (8.7%) and declined among patients older than age 20 years (4.1%), possibly because a larger proportion of older patients are more likely to have "milder" genetic mutations. In most patients, hepatomegaly was an incidental finding noted on examination. Fiegelson et al.[27] from Paris reported a prevalence of 7% of multilobular cirrhosis, 90% appearing before age 14 years. Both of these studies found a slight male predominance, possibly due to the survival advantage in males with CF. Cholelithiasis was present in 0.8% of patients and was unrelated to the presence of cirrhosis. Thirty percent of patients had a transient increase in liver enzymes when multilobular cirrhosis was absent. In a retrospective review of 233 adults (> age 15 years) with CF, 24% were found to have hepatomegaly or persistently abnormal liver blood tests[16]. Thirteen patients underwent cholangiography, two of whom had common bile duct strictures.

Two prospective studies evaluated changes in serum concentrations of AST and alkaline phosphatase in infants and children from North America with CF. Sokol et al. serially studied 99 infants in Denver, Colorado, identified by newborn screening for CF (excluding those with meconium ileus) for the first eight years of life. Researchers found that overall 27% of alkaline phosphatase values and 38% of AST values were above the upper limit of normal for age. The frequency of elevated AST values were: age 6 months = 51%; 12 months = 56%; 2 yr. = 38%; 3 yr. = 23%; 4 yr. = 18% ; 5-6 yr. = 15%; and 6-8 yr. = 13%. The frequency of elevated alkaline phosphatase values were: age 6 months = 39% ; 12 months = 29%; 2 yr. = 25%; 3-6 yr. = 15%; and 7-8 yr. = 6%. The majority of patients had elevations less than 1.5 times the upper limit of normal[29]. Kovesi et al.[30] evaluated the relationship of CFTR mutations to the prevalence of abnormal AST and alkaline phosphatase in 526 CF patients of all ages from Ontario. Abnormal AST or alkaline phosphatase was present in 46% of 267 patients homozygous for the ΔF508 mutation, compared to 20% in 25 pancreatic sufficient patients with mild missense mutations. The prevalence rate was 22%

among all 69 pancreatic sufficient patients, including those with unknown genotypes. Among other genotypes, the prevalence rate was 34-60%. Again, the majority of patients had elevations of AST and alkaline phosphatase less than 1.5 times the upper limit of normal. Although the absolute frequencies of abnormal AST and alkaline phosphatase differed in these two studies, clearly small elevations of liver blood tests are common in CF patients, the significance of which needs to be determined.

Two prospective studies evaluated the frequency of liver abnormalities in CF patients in two other countries. In a prospective evaluation of 153 CF patients ages 4-19 years in New South Wales, Australia, Gaskin et al.[15] found that 30% of patients had hepatomegaly, 9% had elevated liver enzymes without hepatomegaly, and 13% were judged to have multilobular cirrhosis by clinical, biochemical, and imaging criteria. In a similar study, Colombo et al.[4] prospectively evaluated 189 CF patients over three years of age in Milan, Italy. Thirty percent of patients had hepatomegaly, 5.8% had splenomegaly, and 16.9% had abnormal liver enzymes. Liver disease (defined as firm hepatomegaly, persistent elevation of at least two liver enzymes, and abnormal ultrasound features of the liver) was present in 17% of patients. Because the results of these two prospective studies were quite similar, although liver disease was defined differently, the best current estimate for "clinically significant liver disease" in children with CF is approximately 13-17%. A working definition for this would be probable significant hepatic fibrosis leading to some degree of liver dysfunction. However, the presence of hepatomegaly in 30% of patients in both studies suggests that the incidence of significant portal and biliary fibrosis may be higher. Prior historical data had suggested a prevalence of 5% in those older than 12 years, and 10% in those older than 25 years[31]. The true prevalence of histologically identifiable liver disease in CF is unknown.

The prevalence of focal biliary cirrhosis can only be estimated by autopsy series since this lesion is usually clinically silent and may be present with normal liver blood tests. The postmortem incidence was 10% in infants dying in the first 3 months of life, 27% in children dying after 1 year of age[32], and 72% in adults[33]. Unfortunately, these are old data, performed at a time when median survival in CF was low and malnutrition was very common. More recent incidence figures have not been accumulated since the advent of improved treatments and prognosis in CF. Neonatal cholestasis occurs in less than 2% of infants with CF, approximately 50% of the time associated with meconium ileus[34]. Cirrhosis has been reported to develop in 15-20% of such infants. Hepatic steatosis develops in 20-60% of CF patients and has not been correlated with outcome. Micro gallbladder is present in 20-30% of patients[35], and cholelithiasis in less than 1% of patients[26,27,30]. Common bile duct stenosis is a rare complication of CF, occurring in less than 1-2% of patients at most centers. Sclerosing cholangitis is usually diagnosed on the basis of ERCP findings, which can be misleading in the face of biliary cirrhosis and inspissated, thickened biliary secretions. Therefore, the true incidence in CF is unknown, but certainly is low. Cholangiocarcinoma has rarely been observed in CF patients, but must be considered in the adult with new onset of biliary obstruction or with worsening obstructive jaundice, abdominal pain, or weight loss in patients with long-standing hepatobiliary involvement[36] (see Table 1).

V.   CLINICAL FEATURES

One of the common clinical presentations of liver disease in CF is that of an asymptomatic child or adolescent who is found to have hepatomegaly or splenomegaly on routine physical examination. The liver may be firm and nodular, frequently extends >2-3cm below the right costal margin or below the xiphoid, and its enlargement may be limited to either the right or left lobe. Cutaneous signs of chronic liver disease (jaundice, palmar erythema, and spider hemangiomata) are rarely present and peripheral cyanosis or clubbing may be attributed to underlying pulmonary disease. Jaundice is generally limited to CF patients with neonatal cholestasis, cholelithiasis, and end-stage liver disease. Although clinical signs of portal hypertension (splenomegaly, bruising) may be present (<25% of time), gastrointestinal hemorrhage, ascites, porto-systemic encephalopathy, and spontaneous bacterial peritonitis are rarely the presenting features. However, over time, complications of portal hypertension may develop and become the predominate clinical problem related to the liver disease. The other common mode of presentation of CF-related liver disease is elevated serum AST, ALT, alkaline phosphatase, or GGT concentration on routine screening.

Hyperbilirubinemia generally occurs late in the course of liver disease, or from common bile duct obstruction or drug-induced hemolysis. Elevated blood ammonia is only present when liver disease is severe. Prolongation of the prothrombin time may be secondary to severe liver disease or vitamin K deficiency.

In the *neonatal cholestasis* presentation of CF, total and direct bilirubin are elevated, hepatomegaly may be present, and stools have decreased pigment, leading to occasional confusion with the diagnosis of biliary atresia. The cholestatic jaundice resolves over time, however, residual hepatic fibrosis may remain. *Hepatic steatosis* usually presents clinically in a malnourished patient as an asymptomatically enlarged, smooth soft liver without splenomegaly or ascites. *Cholelithiasis* is usually asymptomatic, but may present with right upper quadrant or right shoulder pain, jaundice, nausea and vomiting or pruritus, and elevated alkaline phosphatase, GGT or bilirubin. *Sclerosing cholangitis* generally presents with hepatomegaly and pruritus, occasionally with fevers, and with elevated alkaline phosphatase and GGT; this is rare in CF patients.

As *focal biliary cirrhosis* progresses to *multilobular cirrhosis*, complications of portal hypertension and nutritional deficiencies appear at an unpredictable pace. Portal hypertension may lead to development of esophageal or gastric varices presenting with hematemesis, melena, or iron-deficiency anemia. Ascites, splenomegaly and hypersplenism, encephalopathy, fatigue, and coagulopathy occur late in the course as cirrhosis decompensates. Hepatic synthetic failure is a late finding and is the primary indication for liver transplantation. Impaired bile flow may enhance fat malabsorption leading to increased diarrhea, weight loss, and clinical signs of fat-soluble vitamin deficiencies (vitamin A – night blindness, dry skin rash, xerophthalmia; vitamin D – rickets, osteomalacia, bone fractures; vitamin E - hemolytic anemia, hyporeflexia, ataxia, decreased vibratory and position sensations, ophthalmoplegia; vitamin K – bruising, epistaxis, bleeding)[37].

Cholecystitis presents as abdominal pain, classically in the right upper quadrant, back or right shoulder, and exacerbated by meals. However, poorly localized abdominal pain may also be the cause of chronic cholecystitis in CF. Colicky abdominal pain and/or acute onset of jaundice suggest common bile duct or cystic duct obstruction caused by stones or sludge. Fever, vomiting, and pale stools may also accompany complicated gallstone disease.

Several studies have suggested that the presence of meconium ileus or distal intestinal obstruction syndrome is a risk factor for development of liver disease in CF. Maurage et al.[38] reported this risk factor to be present in 50% of cirrhotic and 14% of non-cirrhotic CF patients. Similarly, Colombo, et al.[4] described an incidence of 35.3% in patients with liver disease, but only 12.3% in non-liver disease CF patients. Despite this apparent association, most CF patients with significant liver disease do not have a history of meconium ileus.

VI. DIAGNOSTIC EVALUATION

In the past, liver disease in CF patients was usually identified because of complications of liver involvement or at surgery/autopsy. Now, asymptomatic hepatomegaly or elevated serum liver enzymes obtained as screening tests are the typical scenarios for suspecting liver disease. The extent and pace of the diagnostic evaluation depend on the suspected severity of liver involvement and presence of complications, as well as the overall clinical status of the patient. Persistent hepatomegaly (increased span of the liver) or splenomegaly, a firm or hard consistency of the liver on palpation, persistently abnormal liver blood tests, complications of portal hypertension, or abnormal liver histology will establish the presence of significant liver involvement. Other common liver diseases that should be considered in the differential diagnosis are listed in Table 2. The evaluation should include several components.

Historical Information

Historical information should describe: a thorough neonatal history; history of jaundice; pruritus; change in activity or school performance; bruising or bleeding; anemia; edema or abdominal swelling; nausea or abdominal pain; change in stool color or frequency; poor weight gain or weight loss; fatigue; medication/ herb/nutrient supplement intake; prior blood product transfusion; alcohol ingestion; and family history of liver disease.

Physical Examination

Physical examination should include percussion and palpation of the entire liver and measurement of the liver span at the right mid-clavicular line.[39] Percussion should be used for the upper border of the liver and the lower border if the liver does not extend below the right costal margin. Record the distance that the liver edge extends below the right costal margin *and* below the xiphoid, and the distance that the spleen extends below the left costal margin. Note the liver edge's texture and firmness; assess the presence of dilated abdominal veins, ascites, and peripheral edema; and identify cutaneous (e.g., palmar erythema, spider hemangiomata, scleral icterus, clubbing) and neurologic features of cirrhosis.

Clinical signs of specific nutrient deficiencies should be sought (e.g., hyporeflexia, ataxia, ophthalmoplegia and decreased position and vibratory sensation for vitamin E; xerosis of the cornea and impaired night vision for vitamin A; bruising or epistaxis for vitamin K, etc.). Nutritional status and cardiac function should be evaluated clinically.

Biochemical evaluation for liver injury and function should include serum AST, ALT, total and direct bilirubin, alkaline phosphatase, GGT, total protein, albumin, prothrombin time, blood ammonia, cholesterol and glucose, and a complete blood count to check for hypersplenism. Fasting serum bile acid concentrations may be an early indicator of the presence of liver dysfunction in CF[40]. However, serum bile acid levels rarely influence clinical decision-making, and should be regarded as a research tool at the present time. Researchers suggest that elevated high molecular mass-alkaline phosphatase is strongly predictive of liver disease[41], that serum glutathione S-transferase B1 activity predicts liver dysfunction in CF[42] and that elevations of serum collagen VI levels correlate with fibrosis in CF[43]; however, these observations remain to be confirmed.

To screen for other causes of liver disease, one should consider obtaining: an antinuclear antibody; anti-smooth muscle antibody and anti-liver-kidney-microsomal antibody (autoimmune hepatitis); alpha-1-antitrypsin level and phenotype; HBsAg and hepatitis C antibody; ceruloplasmin (Wilson's disease); and iron and iron binding capacity (hemochromatosis) when clinically appropriate.

Ultrasonography

Ultrasonography (US) of the liver, biliary tract, gallbladder, spleen, and hepatic vasculature provides useful information and should be performed initially on all patients suspected of having liver disease[35]. US is most helpful to determine the presence of gallstones, common bile duct stones, ascites, and bile duct or hepatic vein dilatation. The test is less useful for the detection and quantification of hepatic fibrosis or cirrhosis because periportal steatosis can appear sonographically similar to focal fibrosis in the liver, both lesions being common in CF. Doppler ultrasonography can detect dilation and flow patterns of hepatic vasculature. Dilated hepatic veins suggest that increased right heart pressure (secondary to pulmonary disease and cor pulmonale) may contribute to hepatomegaly. Portal hypertension is suggested by decreased portal venous flow velocities or reversal of flow (hepatofugal) in the portal veins. However, in one study Doppler ultrasound was found to be an inaccurate assessment of portal hypertension and the presence of varices in CF[44]. Thrombosis of the portal or splenic veins as a cause of splenomegaly can also be detected by ultrasonography.

Hepatobiliary Scintigraphy

Hepatobiliary scintigraphy (iminodiacetic acid [IDA] derivatives) may be useful, both clinically and as a research tool; however, it has limited utility compared to ultrasonography. ^{99m}Tc-IDA derivatives given intravenously are cleared from the circulation by hepatocytes, excreted into the canaliculus and bile ducts, stored in the gallbladder, and excreted into the duodenum. Liver uptake, biliary secretion rates, and mean hepatic residence time can be calculated[45]. Thus IDA scanning may provide quantitative data about liver function in a research setting. Biliary tree obstruction and irregularities, abnormal gallbladder function, and common bile duct stenosis can be determined, albeit with poor resolution compared to cholangiography[46]. Dilatation of the biliary tree cannot be accurately determined by scintigraphy. Scintigraphy may be particularly helpful in demonstrating absence of gallbladder filling that is characteristic of cholecystitis. Therefore, scintigraphy plays a limited role in the clinical evaluation of patients with CF. Although it has been claimed that scintigraphy

should be used to determine if ursodeoxycholic acid therapy should be initiated[47], and that it is of value in monitoring the therapeutic response to this agent[48], neither of these proposals has been validated in controlled clinical trials.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic Retrograde Cholangiopancreatography (ERCP) can reveal strictures, dilation, stones, and other abnormalities of the biliary tree. Because it is invasive and usually requires general anesthesia in children, ERCP is reserved for investigating dilated or narrowed bile ducts identified on ultrasonography or scintigraphy that may be causing clinical symptoms, suspected common bile duct or intrahepatic biliary stones, or suspected biliary colic. Although changes in intrahepatic bile ducts are relatively common in CF liver disease[16], common bile duct stenosis is much less common (<10% of patients with advanced liver disease)[16] than initially reported[15]. ERCP can also be used as a therapeutic intervention to dilate strictures, extract impacted biliary stones, and place biliary stents or perform sphincterotomy to improve common bile duct drainage. It should be pointed out that these procedures should be used only when there are clear clinical indications. In some centers, percutaneous transhepatic cholangiography is used instead of ERCP to delineate and intervene in the biliary tree.

Upper Gastrointestinal Endoscopy

Fiberoptic Upper Intestinal Endoscopy is the most sensitive way to detect esophageal varices, gastric varices, portal hypertensive gastropathy, or gastric and duodenal ulcers. It is indicated for upper gastrointestinal bleeding in a patient with CF. If esophageal variceal hemorrhage is suggested or present at the time of endoscopy, sclerosis or band ligation of varices should be performed endoscopically[49]. It is not recommended that all children or adolescents with suspected or known liver disease undergo endoscopy, since varices in children that have not bled are generally not treated, unless unusual circumstances prevail. In adults with esophageal varices caused by other forms of cirrhosis, beta blocker therapy reduces the risk of the first episode of variceal hemorrhage[50,51,52]. Therefore, endoscopy should be considered in adults with CF and portal hypertension to determine if prophylactic beta blocker therapy should be initiated to prevent variceal bleeding. Side effects of beta blockers are discussed in a later section.

Computerized Tomography

Computerized Tomography of the liver is useful to exclude mass lesions in the liver or biliary tree and may help differentiate hepatic steatosis from fibrosis. However, it is used infrequently in the usual evaluation of suspected liver disease in the CF patient.

Magnetic Resonance Imaging Cholangiography

Magnetic Resonance Imaging Cholangiography is a new non-invasive technique to visualize the biliary tree that has not been tested in CF, but holds promise[53].

Other Imaging Modalities

Abdominal X-rays, upper gastrointestinal contrast X-rays, and oral cholecystography are generally not helpful in evaluating the CF patient with liver disease.

Liver Biopsy

Liver biopsy may be useful to determine if steatosis or focal biliary cirrhosis is the predominant abnormality, to determine the extent of portal fibrosis or cirrhosis, and to demonstrate absence of other lesions. However, not all clinicians believe that liver biopsy is indicated in investigating CF liver disease because of the lack of definitive therapy. When performed in CF patients, percutaneous liver biopsy should only be done after ultrasonographic determination of a safe location for the biopsy, avoiding the right lower lobe of the lung, and aiming towards sonographically involved liver. Percutaneous liver biopsy is contraindicated if significant dilation of hepatic veins (indicative of cor pulmonale) or of intrahepatic bile ducts is present. It is also contradicted if coagulopathy cannot be corrected, if platelet count cannot be increased to above 60-80,000, or if the patient cannot be safely sedated due to lung involvement. Transjugular liver biopsy can be used under these circumstances, if deemed necessary.

VII. RECOMMENDATIONS FOR IDENTIFICATION AND MANAGEMENT OF LIVER DISEASE

A multidisciplinary team approach should be involved in the diagnosis and treatment of hepatobiliary complications of CF. This medical team should include the CF center team, a pediatric (for children or adolescents) or internist (for the older CF patients), gastroenterologist/hepatologist, a nutritionist/registered dietitian, a pediatric or adult surgeon experienced in hepatobiliary surgery, and a radiologist. The approach to managing CF hepatobiliary disease includes: screening for liver disease; medical management; nutritional therapy; management of portal hypertension; management of liver failure; and prophylactic therapy. When the patient has reached the stage of decompensated cirrhosis, it is essential that the medical team has a close working relationship with a liver transplantation center.

Screening for Liver Disease

The first component of managing CF-related liver disease is the identification of those patients with clinically significant liver involvement. Careful **examination and measurement of the liver and spleen** by palpation and percussion should be performed at each clinic visit. Both the right and left lobes of the liver should be palpated. Liver edge palpated more than 2 cm below the right costal margin is abnormal at any age; however, hyperexpansion of the chest in CF can push a normal-sized liver this distance below the costal margin. Therefore, measurement of the liver span at the right mid-clavicular line (in centimeters) is more accurate. The left lobe of the liver should also be palpated below the xiphoid, since it may be the only part of the liver that is enlarged. The liver span should be compared to age-related normative data[39,54]. There is some dispute in the literature as to the normal liver size at various ages. However, the normal mean liver span at the mid-clavicular line is approximately 3.0-5.5 cm at birth, 4-6 cm at 1 year, 5-7 cm at 3 years, 6-8 cm at 5 years, and 7-9 cm at 12 years of life. The upper limit of normal is approximately 1.5 to 2.0 cm above these mean values. In the adult, a liver span of above 12 cm indicates hepatomegaly and below 6 cm atrophy. The texture of the liver edge (soft, firm, hard), which is *more* important clinically than is the absolute size of the liver, should be recorded. A palpable spleen is abnormal; its distance below the left costal margin should also be recorded routinely. A firm or hard enlarged liver, particularly in the presence of splenomegaly, indicates clinically significant liver involvement. With advancing cirrhosis, the liver may shrink and not be palpable or enlarged. Thus, a small liver, when accompanied by splenomegaly, should alert the clinician that significant liver disease is present.

Liver function tests should be obtained yearly in all CF patients. These tests should include serum AST, ALT, alkaline phosphatase, GGT, and bilirubin. It should be noted that none of these tests measures or correlates with the degree of hepatic fibrosis. Nevertheless, if any of these test values is above 1.5 times the upper limit of normal, repeat testing should be performed at shorter intervals (3-6 months). Because fluctuations in the values of these tests are common in CF, only persistently elevated test results should be investigated more completely. Thus, if tests remain elevated for >6 months, without another explanation for the elevation, they are indicative of probable clinically significant liver involvement. Tests of hepatic synthetic function should then be obtained, including serum albumin and prothrombin time (blood ammonia if significant portal hypertension is suspected clinically). It should be noted that in one series, elevated ALT and GGT had only 52% and 50% sensitivity, and 77% and 74% specificity, as predictors of significant hepatic fibrosis in CF patients who underwent liver biopsy[55]. In most surveys, 20 - 30% of CF patients have elevation of at least one of these liver blood tests at a single point in time. Therefore, these tests should be used to screen for those patients who need a more complete evaluation, rather than to be used to diagnose clinically significant liver disease. Exceptions would be those patients with high elevations (>3-5 times the upper limit of normal) of these tests, in whom significant liver disease is likely to be present. Other causes of acute elevation of aminotransferases (hepatitis A virus, CMV, EBV, drugs or toxins, and, when appropriate, hepatitis B and C viruses) or elevated GGT or alkaline phosphatase (gallstones, cholecystitis, bone disease, hyperphosphatasia) should be excluded. If liver blood tests remain persistently elevated without another explanation, then hepatic ultrasound should be performed and consideration given to liver biopsy and other diagnostic modalities discussed previously.

Medical Management

After liver disease has been documented by the presence of hepatomegaly or hepatosplenomegaly, persistently abnormal liver blood tests, abnormal liver biopsy, or abnormalities on imaging studies, it should be determined what caused the liver abnormalities. It is most likely due to hepatic steatosis, hepatic congestion, or the cholestasis/focal biliary cirrhosis/multilobular cirrhosis sequence. Each of these entities will be managed differently and is associated with its own set of complications. Hepatic steatosis is suggested by a palpable softness of the liver, concomitant malnutrition, or fat density seen on CT scanning, and is confirmed by liver biopsy if deemed to be clinically indicated. Steatosis may also be present in conjunction with fibrosis or cirrhosis of the liver, in which case the liver will not be soft to palpation. Hepatic congestion is suggested by clinical signs of cor pulmonale, by dilated hepatic veins on ultrasonography or other imaging studies, or by liver biopsy findings. The cholestasis/cirrhosis sequence is suggested by: elevated fasting serum bile acid concentrations, alkaline phosphatase and GGT; abnormal scintigraphy; fat malabsorption and fat-soluble vitamin deficiencies in patients receiving adequate pancreatic enzyme supplements; firm or hard hepatomegaly; splenomegaly; complications of portal hypertension (ascites, upper gastrointestinal bleeding, spontaneous bacterial peritonitis or porto-systemic encephalopathy); or hepatopulmonary syndrome. This is confirmed by findings on liver biopsy, if deemed necessary.

Hepatic steatosis

Although it is not known what causes hepatic steatosis in the majority of affected CF patients, consideration should be made for evaluating and correcting deficiencies of essential fatty acids, carnitine, or choline, which may lead to steatosis. Medical management consists primarily of optimizing nutritional status of the patient. This should first include a thorough evaluation by a nutritionist, followed by proper pancreatic enzyme supplementation, optimization of dietary intake of calories, protein, fat and essential fatty acids, and fat-soluble vitamin supplementation. Fecal fat losses may need to be quantified during enzyme supplementation. Although steatosis has most often in the past been associated with undernutrition in CF, it also may be present in a well-nourished

patient. In these circumstances, deficiency of the above-mentioned nutrients should be investigated, history of ethanol ingestion and other drugs/toxins should be sought, and the possibility of diabetes mellitus should be evaluated by oral glucose tolerance testing.

Hepatic congestion

Hepatic congestion may lead to "cardiac cirrhosis" or may occur in conjunction with the other liver lesions that result in cirrhosis. Thrombosis of hepatic veins or the IVC should be excluded by Doppler ultrasonography or angiography. Treatment of hepatic congestion centers on therapy to optimize cardiopulmonary function and avoid hypoxia. Generally, AST and ALT are mildly elevated (<2-3x upper limit of normal) in hepatic congestion. Bilirubin may be mildly elevated and prothrombin time may be up to 5 seconds prolonged[56]. Therefore, if AST or ALT is >3 times normal or if alkaline phosphatase or GGT is significantly elevated, the co-occurrence of focal biliary cirrhosis/multilobular cirrhosis is likely and appropriate evaluation and therapy should be instituted (see below). Since percutaneous liver biopsy can be dangerous in this setting, open surgical or transjugular liver biopsy approaches should be considered if biopsy is necessary. Avoiding antioxidant deficiencies that are common in CF, such as alpha tocopherol[57] and beta carotene[58], may be beneficial in reducing ischemia-reperfusion injury to the liver associated with hepatic congestion.

Cholestasis/fibrosis/cirrhosis

These three liver lesions are part of a sequential progression that occurs over a variable period of time; therefore, certain aspects of treatment should be similar for these three lesions. The goal of therapy should be to minimize ongoing liver injury and the progression to cirrhosis, prevent complications of cholestasis, and manage complications of portal hypertension and cirrhosis. No therapy has yet been proven to alter the course of progression to cirrhosis in CF; however, treatment with the hydrophilic bile acid, ursodeoxycholic acid (UDCA), improves the biochemical indices of liver injury and pruritus. UDCA improves bile flow in CF[48], may displace toxic hydrophobic bile acids that accumulate in the cholestatic liver[59], may have a cytoprotective effect[59,60], and may stimulate bicarbonate secretion

into bile[61]. Several open clinical trials demonstrate that AST, ALT, and GGT are reduced when 15-20 mg/kg/day of UCDA are given over 3-12 month periods[59,62-68]. There is no direct evidence as of yet that these reductions are accompanied by delay or reversal of progressive fibrosis, of portal hypertension, or a change in the ultimate outcome in CF. In addition, in other studies there was no improvement in quantitative tests of liver function[66,68] or in nutritional status[69] after 6-12 months of UDCA therapy in CF patients with chronic liver disease. However, the combined data from three studies involving adults with primary biliary cirrhosis (PBC)[70] showed that UDCA therapy did significantly retard the progression of this cholestatic liver disease as evidenced by improved survival free of liver transplantation. It should be noted that the PBC patients with the most advanced liver disease showed a more significant response, approximately a 30% reduction in deaths or need for liver transplant after four years of UDCA therapy. Although the pathobiology of PBC and CF have major differences, the similar biochemical response to UDCA in these two cholestatic disorders and the improved clinical outcome in PBC suggest that UDCA may be of benefit in CF liver disease. Therefore, despite the lack of conclusive evidence that UDCA alters the course and outcome of CF-related cirrhosis, it is prudent to treat CF patients with cholestasis/fibrosis/cirrhosis with 20 mg/kg/day of UDCA in two divided doses[65,71]. There is currently no scientific justification for using UDCA in CF patients who have little or no documented liver dysfunction or portal fibrosis.

It is recommended that patients who are candidates for UDCA treatment be entered into clinical trials, if possible, so that pertinent outcome data can be gathered. Side effects and toxicity of UDCA are unusual and minimal (increased pruritus, diarrhea), and rarely lead to discontinuation of treatment. Monitoring during therapy should include liver blood tests three months after initiating therapy and each 6-12 months thereafter, and serial physical examinations. Repeat liver biopsy is generally not recommended (except in controlled clinical trials) because the focal nature of the liver lesion may make assessment of histological change over time difficult in an individual patient. There are no other proven therapies to retard hepatic fibrogenesis, although maintaining adequate antioxidant status may be important.

Taurine has been suggested as an adjunctive therapy in liver disease because CF patients are commonly deficient in taurine as a result of bile acid malabsorption. Treatment with unconjugated UDCA may increase taurine need for bile acid conjugation, and taurine conjugates of bile acids are better micellar solubilizing agents than the glycine conjugates[63]. However, in a randomized, double-blind trial, Columbo et al.[63] showed no significant effect of taurine supplementation (17-33 mg/kg/day) on liver blood tests or fecal fat excretion in patients with CF liver disease treated with UDCA or placebo. Therefore, taurine is not recommended for the treatment of CF-associated liver disease, although it may be of potential benefit to reduce severe steatorrhea in CF patients.

All patients with CF liver disease should receive a complete immunization series for both the hepatitis A and hepatitis B virus vaccines, unless prior infection with these viruses has been documented.

Cholelithiasis

Cholelithiasis in CF is not responsive to UDCA therapy[72]. If, in the presence of gallstones, clinical symptoms of gallbladder dysfunction or pain are present or liver blood tests remain abnormal, a laparoscopic or surgical cholecystectomy should be performed, unless end-stage liver disease is present. Liver biopsy and intraoperative cholangiogram should always be obtained during any cholecystectomy procedure in a CF patient.

Nutritional Therapy

An important component of the management of liver disease in CF is maintenance of a normal nutritional state. The emphasis is on preserving normal nutritional status and preventing deficiencies rather than on rehabilitating malnourished patients[73]. Patients with significant cholestasis (elevated serum direct bilirubin or serum bile acid concentrations, if measured) may need medium-chain triglyceride (MCT)-containing infant formulas (e.g., Pregestimil, Mead Johnson; or Alimentum, Ross Laboratories) or supplements for older children containing MCT-oil, to promote intestinal absorption of dietary lipid. Protein intake should not be restricted unless decompensated hepatic failure with encephalopathy is present. Energy intake may need to exceed recommendations for CF patients by 20% - 40% depending on the degree of additional fat

malabsorption caused by the cholestasis and the increased oxygen consumption associated with cholestasis and cirrhosis[74].

Monitoring fat-soluble vitamin status every 6 - 12 months is even more important in the presence of liver disease[37] than in the CF patient with pancreatic insufficiency alone[73]. All vitamin doses should be given with a meal and with pancreatic enzyme supplements. Supplementation with the water-soluble form of vitamin E (d-alpha tocopheryl polyethylene glycol-1000 succinate) at a dose of 15-25 IU/kg/day will correct or prevent vitamin E deficiency in this setting. Patients may also need large doses of vitamin D_2 or D_3 (800-1600 IU/day) or 2 - 4 micrograms/kg/day of 25-hydroxyvitamin D (calcifidiol) to normalize serum 25-hydroxyvitamin D concentrations. The optimal dose of vitamin A supplementation has not been determined, however, patients with low serum retinol (<15-20 micrograms/dL) should be supplemented with 2 - 4 times the recommended dietary allowance for age. Serum retinol and retinol binding protein should be monitored to assure adequacy, as well as serum retinyl esters concentration to assess for toxicity (elevated serum retinyl esters). Prothrombin time should be monitored to indirectly assess vitamin K status; 2.5 mg (infants) to 10 mg (adolescents and adults) per dose of vitamin K supplements should be given from twice per week to daily, depending on the response to therapy. Following any change in vitamin dosing, repeat biochemical testing to assure nutritional adequacy should be performed in 1 - 2 months.

Adolescent and adult patients with CF should be counseled about the risks of alcohol use and encouraged to avoid it. Potentially hepatotoxic medications and herbal therapies should also be avoided, if possible.

Management of Portal Hypertension

The development of portal hypertension is a predictable complication of cirrhosis, although the magnitude of symptoms varies depending on how extensive intra-abdominal collateral vessels have developed. *Esophageal varices* may lead to upper gastrointestinal hemorrhage or remain asymptomatic. If bleeding occurs, the patient should be managed as any other patient with an upper GI hemorrhage, i.e., nasogastric tube decompression and lavage, intravenous access, red blood cell transfusion, correction of coagulopathy or thrombocytopenia, intravenous octreotide or vasopressin, intravenous H2-blocker infusion, and careful observation[75] (see Table 3 for drug doses). Upper gastrointestinal endoscopy should be performed when the patient is stable to determine the cause of bleeding. If bleeding persists, endoscopy should be performed to determine the cause and, if esophageal varices are identified as the source of bleeding, then variceal ligation or schlerosis should be performed[49]. If varices are treated, serial sessions of ligation or sclerosis should be performed over several weeks or months until varices are eradicated, followed by periodic (yearly) endoscopies to screen for recurrence of esophageal varices and the need for sclerosis or ligation or the development of gastric varices. *Portal hypertensive gastropathy* is treated with gastric acid inhibitors, sucralfate, and, possibly, beta blockers. *Bleeding gastric varices* may require placement of a transjugular intrahepatic portosystemic shunt (TIPS)[76] or a surgical portosystemic shunting procedure (splenorenal or portocaval interposition shunts)[77] if conservative measures (acid suppression and sucralfate therapy) are ineffective. Beta-blocker therapy may be used to prevent rebleeding of gastric varices and should be used cautiously in patients with reactive airways disease. The placement of a surgical shunt may make liver transplantation more complicated. Patients with severe variceal disease may be considered for liver transplantation (see below). Duodenal or gastric ulcers are treated with gastric acid inhibitors and antibacterial therapy for *H. pylori* if it is present[78].

Chronic therapy with beta blockers has been established as a useful therapy in cirrhotic adults with established varices to prevent the first variceal hemorrhage, resulting in a 10% reduction in risk of bleeding[50,51]. Although one study showed a reduction in splenic pulp pressure in cirrhotic children treated with propranolol, this was not found in those patients with decompensated cirrhosis[79]. Moreover, there have been no randomized, controlled clinical trials of beta blockade in infants or children with varices who have not bled, so the value of this therapy as prophylaxis in children is unknown. Theoretically, this therapy may not be of benefit because children with portal hypertension, compared to adults, may

potentially develop more extensive intra-abdominal collaterals as they grow; children depend more on increase in heart rate than do adults to maintain blood pressure during hypovolemia (e.g., during gastrointestinal hemorrhage); and therapy would have to be continued lifelong. In addition, the possible adverse effects of beta blockade on airway reactivity and the development of clinical depression in children with CF need to be considered. In adults with CF and portal hypertension who have not had gastrointestinal bleeding, documentation of varices by endoscopy and treatment with beta blockers may be of benefit to prevent the first hemorrhage, although this has not been examined directly in CF. In patients with serious, chronic bleeding varices, beta blockade therapy should be considered as an adjunct to prevent further episodes of hemorrhage[80].

Ascites is managed by sequential addition of following (see Table 3 for drug doses): careful salt restriction, diuretic therapy (initially spironolactone and then addition of furosemide), or transjugular intrahepatic porto-systemic shunting, if severe and unresponsive. *Hepatic encephalopathy* is treated by dietary protein restriction, lactulose and/or oral antibiotics, prevention of gastrointestinal bleeding and constipation. Liver transplantation should be considered. Spontaneous bacterial peritonitis is treated with systemic antibiotics after appropriate cultures of peritoneal fluid and blood have been obtained.

Management of Liver Failure

Liver failure in CF patients is rare, however, as the median survival continues to increase, more patients with advanced liver disease will be encountered. Decompensated cirrhosis and hepatic synthetic failure are present when the patient has poorly controlled ascites, prolonged prothrombin time unresponsive to parenteral vitamin K, decreased levels of clotting factor V, elevated blood ammonia, fatigue, or encephalopathy[81]. When these conditions are present, the patient should be referred to a center experienced in the care of chronic liver failure and liver transplantation. The patient should be considered for evaluation for liver transplantation, particularly if pulmonary function is relatively well preserved. Since the waiting time for a cadaver liver donor may exceed one year, patients should be referred for evaluation for transplantation before they are desperately ill. Other measures may be taken to treat symptoms of liver failure, as outlined above. However, prognosis is poor when this stage of decompensated cirrhosis is reached. Liver transplantation in CF results in a one-year survival of approximately 75%-80%[82,83].

Prophylactic Therapy

Although some studies suggest that it is possible to predict patients at high risk for the development of liver injury and cirrhosis in CF (e.g., infants with meconium ileus[4,37]), there is no proven set of predictive criteria for most patients who develop significant liver disease. Thus, instituting any type of therapy to prevent the development of liver disease would require treating all infants and children unless a sensitive and specific biochemical, genetic, or clinical marker of early liver disease is identified. Optimally, prevention of liver disease in CF would be preferable to treating it once identified. However, there are no available data to support UDCA or any other therapy for *prevention* of CF liver disease in infants or children who have no evidence at all of liver disease. Properly controlled, long-term studies to determine if this would be of benefit are needed. Thus, it is currently not recommended to begin UDCA therapy unless definite clinical, biochemical, or histological evidence of liver dysfunction, cholestasis, or fibrosis is present. Abnormal scintigraphy or sonography of the liver should not be used by itself to initiate UDCA therapy, in the absence of other features of liver disease. Measures discussed previously should be taken to prevent other causes of liver injury, such as vaccination against hepatitis A and B viruses, and avoidance of hepatotoxic agents including alcohol.

VIII.   FUTURE TREATMENTS

Earlier intervention in CF liver disease will be possible when there is improved ability to detect early liver involvement in CF and to predict which patients will develop significant liver disease. Thus, clinical, biochemical, or imaging markers of liver injury and fibrosis need to be developed and validated. Controlled, prospective, multi-centered studies must be conducted before prophylactic therapy with any agent can be recommended.

As understanding of the pathogenesis of hepatic

injury and fibrogenesis continues to improve, new approaches to interfering with cellular injury and the recruitment and activation of hepatic stellate cells may lead to prevention of fibrosis[85]. Current results of antioxidant treatment in experimental models of oxidative liver injury are promising[86,87]; however, there is no direct clinical evidence to support this therapy. Further study of the long-term effects of UDCA and related bile acids on fibrogenesis and bile flow will be needed before this therapy can be considered effective.

An exciting possible treatment of hepatobiliary disease in CF is the use of somatic gene transfer. Successful insertion of the normal CFTR gene into normal and CF bile duct cells has been demonstrated in both cell culture[3] and via retrograde infusion into the biliary tree of the rat[84]. It remains to be seen if this approach can alter bile adequately to prevent the development of hepatobiliary lesions and cirrhosis. Strategies for clinically feasible approaches for gene transfer to the biliary tree must be developed before clinical application of this novel approach can be made.

Finally, a better understanding of the ion channels involved in bile secretion and their regulation should lead to new strategies of improving bile composition and flow through stimulation of alternate pathways of chloride and water secretion into bile.

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X. TABLES

TABLE 1

HEPATOBILIARY MANIFESTATIONS OF CYSTIC FIBROSIS

CONDITION	APPROXIMATE FREQUENCY*
• Asymptomatic elevation of liver blood tests	10-35%
• Neonatal cholestasis	<2%
• Hepatic steatosis and steatohepatitis	20-60%
• Focal biliary cirrhosis	11-70%
• Multilobular cirrhosis	5-15%
• Cholelithiasis and cholecystitis	1-10%
• Micro-gallbladder	30%
• Sclerosing cholangitis	<1%
• Common bile duct stenosis	<2%
• Cholangiocarcinoma	Rare

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* see text for age-related differences in approximate frequency

TABLE 2

DIFFERENTIAL DIAGNOSIS OF HEPATOBILIARY DISEASE IN CYSTIC FIBROSIS*

- Infectious hepatitis (Hepatitis A, B, C, D, E viruses, Non A-E virus, CMV, EBV, enteroviruses, others)

- Metabolic liver diseases (alpha-1-antitrypsin deficiency, Wilson's disease, hemochromatosis, tyrosinemia, and others)

- Autoimmune liver dieases (autoimmune hepatitis, primary sclerosing cholangitis)

- Drug-induced or toxic hepatopathy

- Hepatic congestion

- Structural abnormalities (choledochal cysts, bile duct malformations, congential hepatic fibrosis/ polycystic liver disease)
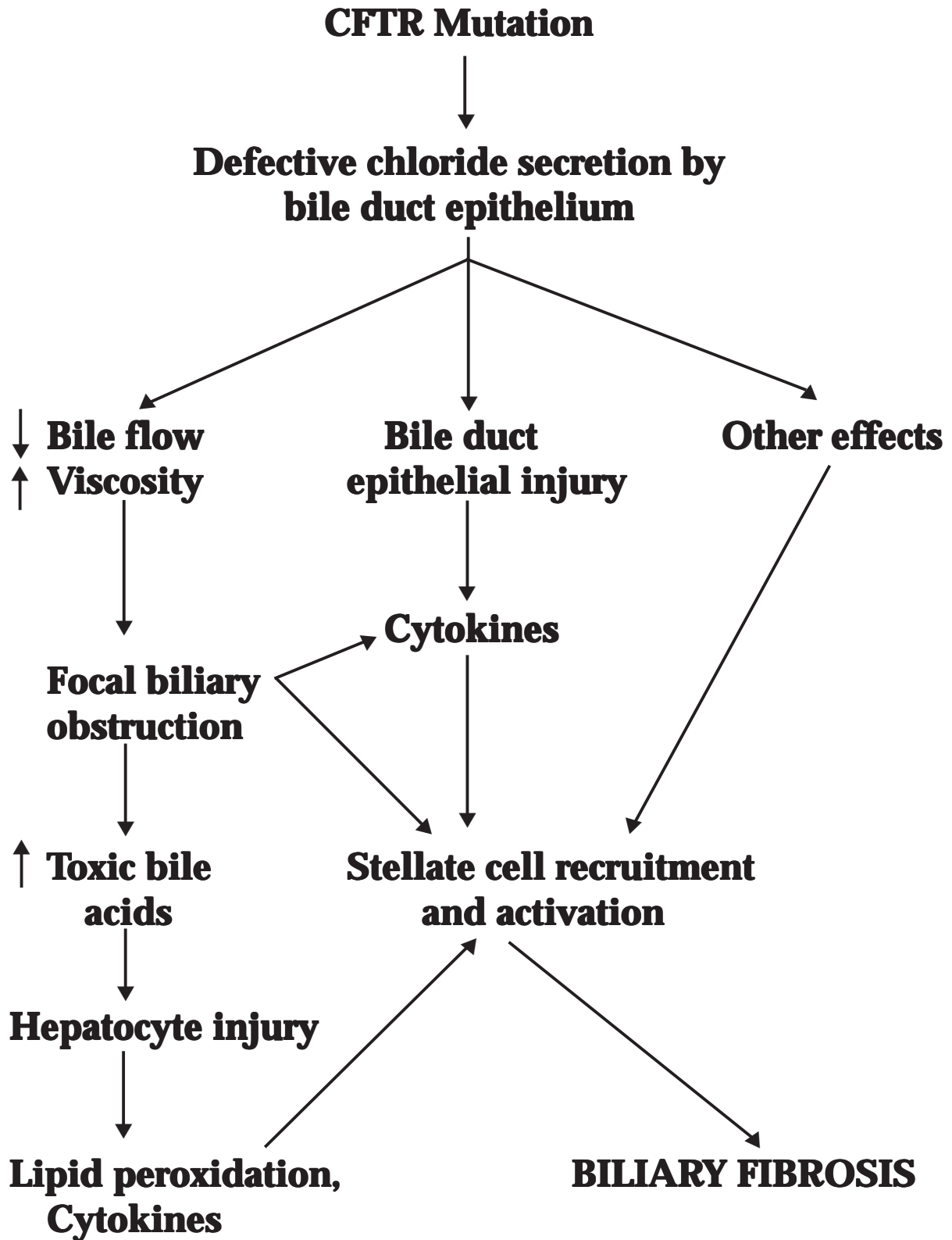
*excludes presentation of neonatal cholestasis

TABLE 3

DRUGS USED IN THE TREATMENT OF CYSTIC FIBROSIS-RELATED LIVER DISEASE

MEDICATION	INDICATIONS	DOSE	TOXICITY
Ursodeoxycholic acid	Cholestasis Pruritus Hypercholesterolemia	15-20 mg/kg/day	Transient increase in pruritus
Rifampin	Pruritus	10 mg/kg/day	Bone marrow suppression, hepatotoxicity
Octreotide	Variceal bleeding	30 μ/m²/hr., IV	Hyperglycemia
Vasopressin	Variceal bleeding	0.1-0.3 U/min., IV	Hypertension, hyponatremia
Propranolol	Prophylaxis for variceal bleeding	2 mg/kg/day (2 doses)	Bronchospasm
Spironolactone	Ascites	3-5 mg/kg/day	Gynecomastia, hyperkalemia
Furosemide	Ascites	1-2 mg/kg/day	Hyponatremia, hypokalemia
Lactulose	Hepatic encephalopathy	1 ml/kg/dose, q4-8 hr. (up to 30 ml/dose)	Diarrhea, hypokalemia
Neomycin	Hepatic encephalopathy	2-4 gm/m² in 4 doses	Nephrotoxicity

XI. FIGURES

FIGURE 1

CFTR Mutation

Defective chloride secretion by bile duct epithelium

↓ **Bile flow**
↑ **Viscosity**

Bile duct epithelial injury

Other effects

Cytokines

Focal biliary obstruction

↑ **Toxic bile acids**

Stellate cell recruitment and activation

Hepatocyte injury

Lipid peroxidation, Cytokines

BILIARY FIBROSIS

FIGURE LEGEND
Proposed pathogenesis of hepatobiliary disfunction, liver injury, and biliary fibrosis in cystic fibrosis. CFTR = Cystic Fibrosis Transmembrane Conductance Regulator gene.

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