

Liver disease in cystic fibrosis

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Purpose of review

This review highlights recent developments in liver disease associated with cystic fibrosis.

Recent findings

The broad spectrum of hepatobiliary problems in cystic fibrosis includes specific alterations ascribable to the underlying defect as well as lesions of iatrogenic origin or that reflect the effects of a disease process occurring outside the liver. Focal biliary cirrhosis, resulting from biliary obstruction and progressive periportal fibrosis, is the most clinically relevant problem, because extension of the initially focal fibrogenic process may lead to multilobular biliary cirrhosis, portal hypertension and eventually liver failure. Cystic fibrosis associated liver disease is presently classified among genetic cholangiopathies and results from lack or dysfunction of the cystic fibrosis transmembrane regulator at the apical membrane of bile duct cells. Major advances have been achieved regarding characterization of natural history, risk factors, diagnostic modalities and treatment options.

Summary

Liver disease is a relatively frequent and early complication of cystic fibrosis. The pathogenesis is apparently multifactorial, with contributions from environmental and genetic determinants. Its impact on quality of life and survival will increase in future years, and its early detection and treatment will become increasingly important issues. Ursodeoxycholic acid is the only treatment currently available, but novel therapeutic options are being evaluated.

Keywords

cystic fibrosis, genetic cholangiopathies, liver disease, liver transplantation, portal hypertension

Introduction

Cystic fibrosis is the most common, potentially lethal genetic disease in white populations, with a reported incidence of approximately 1 in every 3000 live births [1]. It is a multiorgan disease that affects sweat glands, pancreas, lungs and the wolffian ducts in the majority of patients, whereas the liver and the intestine are less frequently involved. The penotypic expression of the disease is extremely heterogeneous in terms of severity and type of organs involved. Lung disease is the primary cause of morbidity and mortality, and results from progressive damage caused by chronic infection with various respiratory pathogens and inflammation, eventually leading to respiratory failure.

When it was first described in 1938, the disease was almost invariably fatal during early childhood, and for many years the basic defect remained unknown. To date, median survival approaches 40 years, but premature death due to respiratory failure remains a major problem [2**]. Improved life expectancy and prolonged follow up of patients with cystic fibrosis have allowed direct observation of an increasing number of liver-related events. A broad spectrum of hepatobiliary manifestations have been recognized that include specific alterations ascribable to the underlying cystic fibrosis transmembrane regulator (CFTR) defect as well as lesions of iatrogenic origin or that reflect the effects of a disease process occurring outside the liver [3] (Table 1). This review highlights recent developments in liver disease associated with cystic fibrosis and describes recent trends in treatment options.

The focal biliary cirrhosis/multilobular cirrhosis continuum

The typical hepatic lesion of cystic fibrosis is focal biliary cirrhosis, which results from biliary obstruction and progressive periportal fibrosis. This is the most clinically relevant cystic fibrosis associated hepatic pathology, because extension of the initially focal fibrogenic process may lead to multilobular biliary cirrhosis, portal hypertension and related complications [4] (Fig. 1). Unlike pulmonary and pancreatic diseases, which affect about 90% of cystic fibrosis patients, liver disease develops in no more than one-third of patients with cystic fibrosis. Nevertheless, liver disease and liver failure remain the single most important nonpulmonary cause of death, accounting for about 2.5% of overall cystic fibrosis mortality [5].

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Abbreviations

CFTR cystic fibrosis transmembrane regulator
UDCA ursodeoxycholic acid

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Table 1 Major hepatic manifestations in cystic fibrosis

Type of lesion	Clinical manifestation	Frequency (%)
Specific alterations ascribable to the underlying CFTR defect	Focal biliary cirrhosis	20–30
	Multilobular biliary cirrhosis	10
	Portal hypertention	2–5
	Neonatal cholestasis	Rare
	Sclerosing cholangitis	Rare
	Micro-gallbladder	30
	Cholelithiasis	15
Lesions of iatrogenic origin	Liver steatosis	23–67
	Drug hepatotoxicity	Undefined
Lesions reflecting the effects of a disease process that occurs outside the liver	Hepatic congestion	Rare
	Common bile duct stenosis	Rare

CFTR, cystic fibrosis transmembrane regulator.

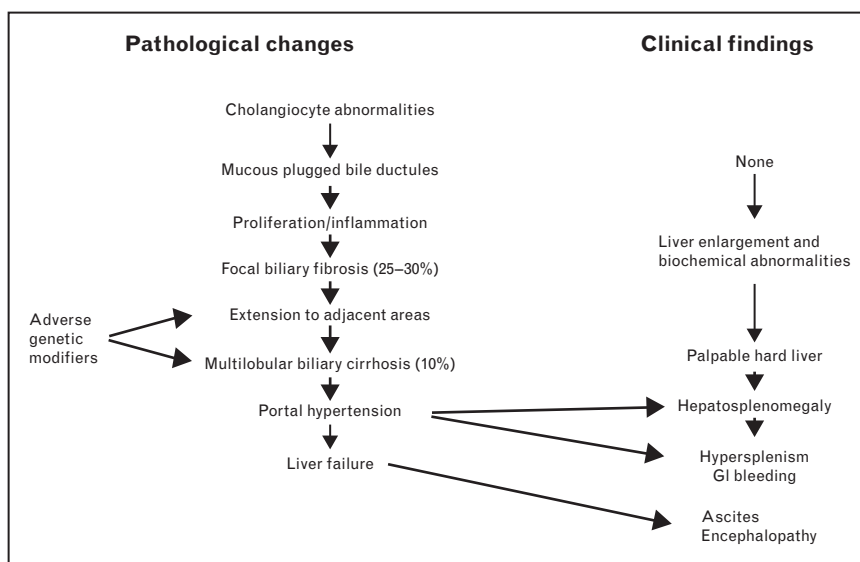
Pathogenesis

Cystic fibrosis associated liver disease is presently classified among genetic cholangiopathies [6]. In the hepatobiliary system, CFTR is expressed exclusively at the apical membrane of cholangiocytes and gallbladder epithelial cells, and not in hepatocytes [7]. At this level, CFTR regulates the fluid and electrolyte content of bile. Its absence or dysfunction in cystic fibrosis patients is considered the central step in the pathogenetic sequence of cystic fibrosis associated liver disease, which may therefore represent the first example of an inherited liver disease resulting from impaired secretory function of the biliary epithelium and ductal cholestasis. Ultrastructural abnormalities of cholangiocytes (with irregular shapes, necrosis and periductular collagen deposition) have consistently been documented in patients with cystic fibrosis [8], suggesting that injury to bile duct cells may indeed represent the primary event in the development of periportal fibrosis.

CFTR-related abnormalities in mucin secretion may also contribute to increased bile viscosity in cystic fibrosis patients [9,10] and lead to bile duct plugging with eosinophilic material, which is among the early histological changes found in infants and children with cystic fibrosis [11]. This process may increase susceptibility of the biliary epithelium to damage by cytotoxic compounds excreted into bile and to attack by microbial pathogens. Retention of endogenous hydrophobic bile acids may be responsible of secondary hepatocyte injury, with release of proinflammatory cytokines, growth factors and lipid peroxide products, and activation of hepatic stellate cells to synthesize collagen. The progression from cholestasis to focal and eventually multilobular cirrhosis may take years to decades to occur, and it should be viewed as a continuum [4] (Fig. 1).

In summary, the evidence currently available suggests that liver disease in cystic fibrosis is related to the cystic

Figure 1 Evolution of liver disease in cystic fibrosis



GI, gastrointestinal.

fibrosis basic defect at the hepatobiliary level. It remains to be determined, however, why only one-third of patients with cystic fibrosis develop liver disease and why liver disease exhibits a great degree of variability in terms of severity. In a minority of patients, often in the pediatric age range, liver disease may progress rapidly and represent the main clinical problem. The factors responsible for such rapid evolution are still undefined. No specific CFTR mutation has been associated with its presence and severity [12,13], suggesting a multifactorial pathogenesis.

The relevance of severity of abnormalities in liver biochemistry or detection of nonspecific ultrasonography findings (fatty infiltration or increased liver texture) to the development of severe liver disease should be further explored. Steatosis has been reported in cystic fibrosis patients of any age, with prevalence figures ranging between 23% and 67%, often in association with severe malnutrition or selective nutritional deficiencies (essential fatty acids, carnitine and choline) [14,15]. It has thus far been considered a benign condition, without proven relationship to subsequent development of cirrhosis, but in a few patients steatosis was recognized as the first step in the progression toward more severe hepatic lesions. Studies underway examining the role played by nonalcoholic steatohepatitis as a cause of cirrhosis in children [16] and adults [17] may lead to reconsideration of this issue in the future.

Several factors have been recognized to be significantly associated with development liver disease, including pancreatic insufficiency, severe genotype, male sex, history of meconium ileus and age at diagnosis of cystic fibrosis [12,13,18–20] (Table 2). The roles played by some of these factors (particularly meconium ileus) as a risk factor remain controversial, however [13,14,20].

Finally, there is mounting evidence that genetic factors inherited independently from the CFTR gene (modifier genes) could modulate the clinical expression and severity of liver disease in cystic fibrosis [25] and that polymorphisms in genes that upregulate inflammation,

fibrosis, or oxidative stress may be involved [26**]. A complex multigenic inheritance may be present, with interactions between various genes (α_1 -antitrypsin deficiency, transforming growth factor- β cytokine, mannose-binding lectin 2, and glutathione S-transferase) [27–29]. Identification of genetic modifiers is a priority because it may allow identification of those patients who are at risk at the time of diagnosis of cystic fibrosis and permit early institution of prophylactic strategies.

Prevalence of liver disease

There are marked differences in the reported prevalence of cystic fibrosis associated liver disease, which may be explained by the use of different diagnostic criteria and may depend on the population studied. Prevalence appears to increase through childhood into mid-adolescence, with no significant increase thereafter [21]. More recently, prospective studies have been carried out to assess incidence and risk factors for the development of liver disease. Long-term follow up of different cohorts of cystic fibrosis patients whose hepatic status was carefully monitored has indicated that the cumulative incidence of liver disease ranges between 27% and 35%, without incident cases after the age of 18 years [14,18,30].

Overall, the data suggest that liver disease is an early complication of cystic fibrosis, and that the mechanisms and risk factors for liver damage are present from early childhood.

Natural history and clinical features

Liver disease associated with cystic fibrosis usually develops before puberty, and it is often asymptomatic and slowly progressive. The most common presentation is the occasional finding of hepatomegaly on routine physical examination, which is often but not always associated with abnormalities of liver biochemistry.

Multilobular biliary cirrhosis is believed to develop sequentially from focal biliary cirrhosis, but this progression occurs only in about 10% of patients [14]. As in other liver diseases characterized by initial involvement

Table 2 Risk factors for the development of liver disease in cystic fibrosis patients

Risk factor	Presumed mechanism/comment	References
Pancreatic insufficiency	Intestinal malabsorption and poor nutritional status	[12,13,18,19]
Severe genotype	Severe genotype Complete loss of CFTR function Necessary but not sufficient condition	[12,13,18,19]
Male sex	Protective effect of hormonal factors (oestrogens?)	[18,21–23,24**]
History of meconium ileus	Abdominal surgery with small bowel resection Poor nutrition in early life Prolonged total parenteral nutrition Genetic modifiers?	[18,19,23]
Age at diagnosis of cystic fibrosis	Diagnostic delay and poor nutrition status	[20]

CFTR, cystic fibrosis transmembrane regulator.

of bile ducts and not of hepatocytes, liver failure is a late event. In contrast, the haemodynamic consequences of cirrhosis are often prominent, favouring early development of portal hypertension [22,23,31]. A recent case-control study evaluated the prognostic implications of variceal bleeding in cystic fibrosis [31]. In a group of 18 adult patients followed at a single cystic fibrosis centre, bleeding occurred at a median age of 20 years (range 9.7 to 30.9 years). Median survival after the first episode of bleeding was 8.4 years, as compared with a 1-year survival of only 34% in the general cirrhotic population [32], suggesting that a history of bleeding in the absence of decompensated cirrhosis may not represent a markedly adverse prognostic factor in cystic fibrosis [31].

Clinical data obtained through prospective studies [14,18,30] have confirmed that liver disease in cystic fibrosis progresses slowly in general. This was also documented by means of histological evaluation [14].

These studies have also indicated that liver disease does not expose cystic fibrosis patients to greater risk for severe pulmonary disease or other major outcome events, including mortality from any cause.

Impact of end-stage liver disease in cystic fibrosis

The impact of advanced liver disease on pulmonary function and nutritional status of cystic fibrosis patients is becoming increasingly evident. Once cirrhosis and portal hypertension are established, cystic fibrosis patients are at risk for developing several extrahepatic complications, including malnutrition, hepatic osteodystrophy and deterioration of pulmonary status.

The pathogenesis of malnutrition in cystic fibrosis patients with liver disease is multifactorial and involves increased resting energy expenditure, malabsorption (due to the combined effect of cholestasis and pancreatic insufficiency), and abnormal intake and metabolism of nutrients [33]. Many cystic fibrosis patients begin to exhibit decompensated liver disease in adolescence, when glucose intolerance and diabetes mellitus are more likely to develop; in addition, advanced liver disease may induce insulin resistance and thus represent a major risk factor for the development of cystic fibrosis related diabetes [34[•]].

The presence of liver disease does not appear to be an additional risk factor for the development of abnormal bone mineralization [35[•]]. Severe osteopenia, however, has been documented in a group of patients with multilobular cirrhosis and portal hypertension, which was significantly ameliorated after transplantation but not after conservative management [36], probably because

of restoration of hepatic function and bile flow after transplantation.

With regard to pulmonary status, cirrhosis and portal hypertension can adversely affect respiratory function because of organomegaly, ascites-induced diaphragmatic spinting and intrapulmonary shunting, leading to recurrent respiratory infections from multiresistant bacteria, frequent hospital admissions and significant deterioration in quality of life.

Diagnosis

Evidence of liver disease in cystic fibrosis patients is often subclinical until the most advanced stages are attained. Therefore, early detection can be difficult and the condition is often under-diagnosed. No test specifically directed at evaluation of biliary cell dysfunction is yet available, and therefore diagnosis is still based on clinical examination (with measurement of liver span at the mid-clavicular line) and on a combination of biochemical tests and imaging techniques, particularly ultrasonography.

It should be recalled, however, that in cystic fibrosis biochemical abnormalities are frequently mild or intermittently present, and have shown low sensitivity and no correlation with histological findings [37]. Not infrequently, cystic fibrosis patients with multilobular biliary cirrhosis have completely normal liver biochemistry. Isolated elevation of serum transaminase levels with normal concentrations of enzymes related to cholestasis (γ -glutamyl transpeptidase and alkaline phosphatase) suggests the presence of steatosis, which should be recognized and followed up, after correction of nutritional deficiencies if present.

Histological assessment, which represents the 'gold standard' in the diagnostic work up of many chronic liver diseases, may under-represent the extent of disease because of a patchy distribution of lesions [37]. On the other hand, cases have been reported of paediatric patients in whom liver disease was the only manifestation of cystic fibrosis, and the diagnosis was made only following histological examination of a liver specimen obtained by biopsy or at autopsy [38[•]]. Liver biopsy may provide important information on the type of the predominant lesion (steatosis or focal biliary cirrhosis), extent of portal fibrosis, rate of progression of liver disease and response to treatment.

Imaging techniques (ultrasonography, magnetic resonance and computed tomography) have progressively gained importance for the diagnosis of hepatobiliary abnormalities in cystic fibrosis, and recently some characteristic findings in patients with cystic fibrosis have been described [39[•],40[•]]. Ultrasound scanning of the

hepatobiliary system can reliably distinguish between different patterns of the disease, such as fibrosis, cirrhosis, portal hypertension, ductal abnormalities and fatty infiltration, and is recommended as the most appropriate initial noninvasive method of investigation. A rather peculiar pattern of lobular fatty infiltration has been also described in cystic fibrosis patients; pseudomasses appear as lobulated fatty structures, 1–2 cm in size, causing heterogeneity in the liver parenchyma [39^{*}]. They have been described as hyperechoic areas with hypoechoic rims, with the latter corresponding to the normal liver parenchyma squeezed in between these fatty areas [39^{*}].

A criterion for diagnosis of periportal fibrosis has been established, namely presence of hyperechoic periportal tissue with a thickness in excess of 2 mm [39^{*}]. Abnormal echogenicity frequently precedes clinical and biochemical manifestations of liver disease, suggesting that routine ultrasonography may be a valuable marker of early liver disease in cystic fibrosis [41,42]. A simple echographic scoring system based on coarseness of liver parenchyma, nodularity of the liver edge and increased periportal echogenicity has been proposed for use in hepatic follow up of these patients [43]. An alternative scoring system that evaluates additional components of liver disease is presently under evaluation [44].

Magnetic resonance cholangiography can document abnormalities of the intrahepatic and extrahepatic biliary tree noninvasively. Cholangitic lesions (beading, narrowing, focal stricturization and dilatation) were detected in all patients with liver disease and in half of those without clinically apparent liver disease [45]. Another study identified cholangitic lesions in 40% of cystic fibrosis patients, and 12% progressed to multilobular biliary cirrhosis [40^{*}]. Overall, the data suggest that magnetic resonance cholangiography may be employed for early detection of intrahepatic biliary tract involvement, which is not achievable with other noninvasive methods.

Hepatobiliary scintigraphy, using third-generation iminodiacetic acid derivatives as tracers, can document a typical picture of biliary drainage impairment, with dilatation of intrahepatic and extrahepatic bile ducts and delayed biliary excretion and intestinal appearance of the tracer [46]. Scintigraphy also provides functional information and has been employed to document time-related progression of liver disease [47] and to monitor response to treatment with ursodeoxycholic acid (UDCA) [48].

Hepatic follow up of cystic fibrosis patients

Regular monitoring of hepatic status should be conducted in all patients with cystic fibrosis, with liver biochemistry and ultrasound scanning included in the routine annual schedule. In patients with cirrhosis it is

prudent to determine α -fetoprotein levels annually in order to detect possible development of hepatocellular carcinoma [49,50]. Upper gastrointestinal endoscopy can detect the presence of esophageal varices and portal hypertensive gastropathy, and should be performed at least annually in patients with portal hypertension.

Management of cystic fibrosis-associated liver disease

Because of decreasing mortality from extrahepatic causes, management of liver disease in cystic fibrosis patients is becoming a relevant clinical issue. At present, management of cystic fibrosis associated liver disease depends on clinical manifestations. Oral bile acid therapy is generally begun early in the course of disease when the patient is asymptomatic, whereas end-stage liver disease often requires a complex and multidisciplinary approach, including a variety of surgical interventions.

Bile acid therapy

Oral bile acid therapy, aimed at improving biliary secretion in terms of bile viscosity and bile acid composition, is currently the only available therapeutic approach for cystic fibrosis associated liver disease.

UDCA administration can oppose several of the mechanisms that are involved in cholestasis-induced liver injury [51]. The changes induced in bile acid composition through replacement and/or displacement of hydrophobic endogenous bile acids may prevent perpetuation of liver damage caused by their retention within the hepatocyte during cholestasis. Other mechanisms of action may be involved, including direct cytoprotection by UDCA of biological membranes, a protective effect against apoptosis induced by endogenous bile acids, and stimulation of bile secretion by hepatocytes and bile duct epithelial cells [51]. Recent data indicate that the beneficial effects of UDCA in cystic fibrosis associated liver disease may mainly be related to stimulation of chloride secretion through calcium-dependent chloride conductance and to concomitant reduction in mucin secretion [52].

The optimal daily dose of UDCA (20 mg/kg body weight) [53] is higher than that conventionally used in other cholestatic liver diseases. This is probably because of poor intestinal bile acid absorption in cystic fibrosis patients.

Although no systematic study addressing the safety of UDCA in cystic fibrosis-associated liver disease and other paediatric liver diseases has yet been reported, UDCA is generally well tolerated and without significant adverse effects. Beneficial effects have been documented in terms of liver biochemistry [54], liver histology [55], hepatic excretory function, biliary drainage [48] and

essential fatty acid status [56]. The latter may have potential extrahepatic implications because essential fatty acid deficiency occurs in cystic fibrosis as a result of a specific defect in fatty acid metabolism, producing a membrane lipid imbalance that in turn may influence inflammatory status and the severity of pulmonary disease [57].

Although no data are available regarding clinically relevant events and survival [58], UDCA is currently widely used to treat cystic fibrosis associated liver disease. Asymptomatic patients with early-stage liver disease are more likely to benefit from UDCA administration. Identification of cystic fibrosis patients who are at risk for development of liver disease would allow to determine whether UDCA also has a role to play in the prevention of liver disease.

Treatment of portal hypertension and end-stage liver disease

In cystic fibrosis patients with more advanced liver disease, severe portal hypertension and hypersplenism are the most relevant problems. The efficacy of α -receptor blockade has not been evaluated in cystic fibrosis because of the adverse effects of α -blockers on airway reactivity.

Variceal bleeding may require sclerotherapy or preferably variceal ligation during the acute episode; endoscopic treatment is successful in most cases [31], but it must be repeated periodically until varices are eradicated. In some patients gastric variceal bleeding or portal hypertensive gastropathy develop and may require additional therapeutic interventions. No studies have assessed prospectively the indications and actual benefits of different therapeutic interventions and their optimal timing for cystic fibrosis patients with portal hypertension and hypersplenism.

Transjugular portosystemic shunt (TIPS) has been employed as a short-term method for achieving portal decompression in patients awaiting liver transplantation [59]. Elective surgical portosystemic shunt is indicated in patients with refractory bleeding, preserved liver function and without severe pulmonary disease, and has allowed prolonged postoperative survival of up to 15 years [23].

Splenectomy and partial splenectomy (with conservation of the upper pole of the spleen) have been performed in cystic fibrosis patients with variceal bleeding and/or massive splenomegaly [60,61,62]. The efficacy of these procedures requires further evaluation.

Liver transplantation is an effective therapeutic option for cystic fibrosis patients with end-stage liver disease. The 1-year-survival rate after transplantation in cystic fibrosis patients is approximately 90% [63], with bene-

ficial effects on lung function, nutritional status, body composition and quality of life in most cases [36]. A 5-year survival rate of 75% has been reported, with late mortality generally being related to progression of pulmonary disease [64]. Survival data for combined liver–lung transplantation are comparable to those observed in other groups of patients receiving lung transplants, with reported 1-year and 5-year actuarial survival rates of 85.7% and 64.2%, respectively [65].

Despite the fact that liver transplantation is increasingly performed in cystic fibrosis as a result of improved survival, evidence-based specific guidelines regarding indications for and timing of this procedure are not yet available. As stated above, liver failure is a late event, but end-stage liver disease may have a major impact on cystic fibrosis. Some authors [66,67] believe that liver transplantation should be considered only in those patients with hepatocellular failure, with the assumption that if hepatocellular function is good then survival is dependent almost exclusively on the progression of respiratory disease [31]. Others [63,64,68] are more inclined to perform transplantation earlier, before signs of hepatocellular failure are prominent, because the risk for premature death may be increased in patients with cirrhosis and portal hypertension [22]. Recently, a poll of European cystic fibrosis and transplant centres was carried out in order to obtain information on current practice and outcome following liver transplantation in cystic fibrosis patients in Europe [24**]. In the majority of cases the decision to perform transplantation was based on the contemporaneous presence of various factors and was generally conducted before development of end-stage liver disease. Specific clinical scores that consider not only features of portal hypertension, hepatocellular function and hypersplenism, but also nutritional and pulmonary status have been devised to evaluate the need for and timing of liver transplantation in cystic fibrosis patients, but they require further evaluation [63,68].

Conclusion

Liver disease is a relatively frequent and early complication of cystic fibrosis. The pathogenesis appears to be multifactorial, with variable contributions from environmental and genetic determinants. With improved life expectancy of cystic fibrosis patients, the impact of liver disease on quality of life and survival will increase. UDCA is currently the only accepted treatment for liver disease in cystic fibrosis.

Several therapeutic strategies may become available, including liver-targeted gene therapy [69] and pharmacological correction of the defective ion transport function [70,71]. Docosahexaenoic acid supplementation has yielded significant improvement in severity of liver disease in a long-lived CFTR knockout mouse model,

with a striking reduction in the degree of periportal inflammation [72[•]]. Its beneficial effect, which may be related to inhibition of cytokines and/or eicosanoid metabolism, must be confirmed in clinical studies.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 557).

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