Intestinal bile acid reabsorption in health and disease

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CHAPTER 2

Diagnosis, follow-up, and treatment of cystic fibrosis-related liver disease

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Abstract

Purpose of review

To provide an insight and overview of the challenges in the diagnosis, follow-up, and treatment of cystic fibrosis-related liver disease (CFLD).

Recent findings

The variable pathophysiology of CFLD complicates its diagnosis and treatment. A 'gold standard' for CFLD diagnosis is lacking. Over the past years, new techniques to diagnose features of CFLD, such as transient elastography, have been investigated. While most of these tests confirm CF-related liver involvement (CFLI), they are, however, not suitable to distinguish various phenotypical presentations or predict progression to clinically relevant cirrhosis or portal hypertension. A combined initiative from the European and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN, respectively) has been started, aimed to obtain consensus on CFLD criteria and definitions. Currently, only ursodeoxycholic acid (UDCA) is used in CFLD treatment although it has not been convincingly demonstrated to change the natural course of the disease . Drugs that directly target CFTR protein dysfunction show promising results, however more long-term follow-up and validation studies are needed.

Summary

CFLD is an umbrella term referring to a wide variety of liver manifestations with variable clinical needs and consequences. CFLD with portal hypertension is the most severe form of CFLD due to its significant implications on morbidity and mortality. The clinical relevance of other CFLI is uncertain. Consensus on CFLD definitions is essential to validate new diagnostic tools and therapeutic outcome measures.

Key points

- The current diagnostic CFLD criteria are effective at identifying *liver involvement* in CF or, in other words, Cystic Fibrosis Liver Involvement (CFLI). However, they do neither distinguish between phenotypical presentations nor predict progression to cirrhosis or portal hypertension once CFLI has been identified.
- Among the new techniques for CFLD diagnosis and follow-up, transient elastography (TE) and acoustic radiation force imaging (ARFI) show some promising results, although not as single diagnostic tests.
- Currently, ursodeoxycholic acid (UDCA) is the only widely used treatment for CFLD despite the lack of convincing studies showing long-term efficacy.
- Novel treatments directly targeting the underlying CFTR defect or the bile acid metabolism show potential benefits in (pre)clinical studies, but clinical data regarding relevant key outcomes on CFLD are not yet available.

Introduction

With improvements in the treatment of pulmonary complications of cystic fibrosis (CF), gastrointestinal and hepatological problems are increasingly affecting morbidity. Hepatic involvement in CF is common and has variable manifestations. The term CFLD is used rather non-specifically and can refer to a multitude of hepatobiliary problems, ranging from (neonatal) cholestasis, biliary tract disease, abnormal liver biochemistry to histological changes such as steatosis and cirrhosis, and complications such as portal hypertension (1). CFLD with portal hypertension is the most severe form and accounts for 3.3% of CF-related mortality (2). CFLD often presents early in life with a median age of 10 years at diagnosis (3). Recently Koh *et al.* suggested that adult-onset CFLD might be more common than previously thought (4).

The mechanisms underlying CFLD are not clear, and various pathophysiological mechanisms may underlie the different hepatobiliary changes grouped together in CFLD. In the liver, CFTR is exclusively expressed in cholangiocytes lining the bile ducts (5).The most widely accepted hypothesis states that loss of CFTR function occludes the small bile ducts causing focal biliary retention, ultimately leading to focal biliary cirrhosis, which in some cases progresses to multilobular cirrhosis and portal hypertension (1). Recently, inflammation secondary to intestinal translocation of bacterial products has been proposed as a crucial factor in CFLD pathophysiology (6). Others suggest vascular changes, namely obliteration of portal vein branches with fibrosis leading to portal hypertension (7).

The variable pathophysiology and phenotype of CFLD make its diagnosis and optimization of treatments challenging. This review analyzes the most recent advances in the diagnosis, follow-up and treatment of CLFD. The need for a consensus on the definition of CFLD for the validation of new diagnostic tools and treatments will be highlighted.

Diagnosis and follow-up

Due to the variable manifestations and the pathophysiology of CFLD, a diagnostic gold standard is unavailable. Yet, the early diagnosis of CFLD which has the potential to develop into cirrhosis and/or portal hypertension, is essential to offer sufficient clinical follow-up and potential preventive treatment.

Classification, definition and diagnostic criteria

The definition and classification of the spectrum of hepatobiliary disease in CF strongly influence how the diagnosis of CFLD is made. The phenotypic CFLD classification (Table 1, adapted from Flass and Narkewicz (8)), based on a consensus among hepatologists at a meeting of the North American CF Foundation in 2007, includes three main categories: 1) CF-related liver disease (CFLD) with cirrhosis/portal hypertension, 2) CF-related liver involvement (CFLI) without cirrhosis/portal hypertension and 3) Preclinical: no evidence of liver disease. The third category has no clinical relevance and was included only for research purposes.

Debray and Colombo (1) proposed diagnostic criteria that have been widely used for the assessment of novel diagnostic tools. According to these, CFLD is diagnosed when at least two of the following features are present: 1) hepato/splenomegaly, 2) abnormal liver function tests, 3) hepatobiliary abnormalities in ultrasound studies or signs of portal hypertension or biliary tract abnormalities (bile duct dilatation). It is apparent that using these criteria a heterogeneous group of CFLI is included in CFLD diagnosis. Very recently, new criteria that reflect the recent developments in diagnostic techniques for CFLD were proposed by Koh *et al*. (4). These criteria do not include findings from physical examination, but rather signs of cirrhosis or diffuse liver disease on radiological imaging, abnormal findings in transient elastography (TE) and elevated fibrosis markers such as the AST/ Platelets-Ratio-Index (APRI). These criteria permit more frequent diagnosis of CFLI rather than CFLD with (an increased risk of developing) cirrhosis or portal hypertension. Finally, at the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) monothematic conference on CFLD (Paris 2016), efforts have been started to reach a uniform international definition and classification of CFLD. Both the Debray-Colombo criteria and the criteria by Koh *et al.* include a heterogenous group of liver involvement. It is not clear whether and how these types of CFLI relate to clinically relevant cirrhosis or portal hypertension. Therefore, this review will be structured based on the phenotypical classification described by Flass and Narkewicz. (8).

Diagnosis of CFLD with cirrhosis/portal hypertension

CFLD with cirrhosis and/or portal hypertension is clinically the most relevant presentation because it carries a direct risk of morbidities, such as severe bleeding from esophageal varices, and mortality. Additionally, CFLD with portal hypertension is often directly clinically recognizable, unlike many other types of CFLI. In the following section various tests with their sensitivity and specificity values will be discussed. The values presented are measured in CF patients and cannot necessarily be translated to other forms of liver cirrhosis or portal hypertension.

The gold standard for the diagnosis of liver fibrosis and end-stage cirrhosis is by liver biopsy, but this requires an invasive procedure with inherent risk, which strongly limits its broad application. The use of biopsy-derived histopathology is also hampered by the focal nature of CFLD lesions (1). Its sensitivity can be increased by performing large dual pass biopsies (sampling two rather than one area of the liver) and more quantitative histochemical analyses (9).

In clinical practice, the diagnosis of cirrhosis is frequently based on ultrasound findings of a heterogeneous nodular liver with irregular margins. The diagnosis of portal hypertension is highly suspected in the presence of splenomegaly and persistent or progressive thrombocytopenia (platelet count <150-200 10^9/l). In CF, portal hypertension has also been reported without the histologic or radiological signs of cirrhosis (7,10). Liver function tests (LFTs) like transaminases have no specific value for the diagnosis of portal hypertension or cirrhosis (9) and may even be normal in the presence of multilobular cirrhosis (1).

It was reported that the degree of histological liver fibrosis can predict the development of portal hypertension in CFLD (9). Using non-invasive tests to assess the extent of liver fibrosis is a long-standing goal to avoid the risks of liver biopsies. New non-invasive techniques to assess liver fibrosis include *transient elastography (TE)* and *acoustic radiation force impulse (ARFI).* TE is a non-invasive procedure that measures liver stiffness, which correlates to the degree of fibrosis. *ARFI* quantification is a variant of TE, with the advantage of being incorporated in conventional ultrasound equipment. TE was reported to be fairly accurate (sensitivity 67-89%; specificity 82-98%) in detecting portal hypertension in several studies (11–14) and cirrhosis in one study (sensitivity 100%; specificity 75%) (15), which also assessed ARFI for the same purpose (sensitivity 100%; specificity 62.5% in the right liver lobe). APRI, a combined measure calculated as ((AST/ULN AST) x 100/Platelets), was similarly accurate in detecting portal

hypertension (sensitivity 67-88%; specificity 89-93%), (11,13). However, for both TE and APRI, highly variable cut-off values were used.

Hepascore (which combines age, gender, gamma-glutamyltransferase (GGT), alpha-2-macroglobulin, total bilirubin and hyaluronic acid levels) and Forns index (which combines age, GGT, cholesterol, and platelet count), performed well in detecting portal hypertension (Hepascore: sensitivity 88%; specificity 83%, Forns index: sensitivity 88%; specificity 86%), but their performances have only been reported in one study so far (13). Large variations in cut-off values in these studies may be explained by the small sample sizes utilized. In a large pediatric cohort, persistently high-normal values of GGT (>35U/L) were associated with the diagnosis of cirrhotic CFLD within 2 years (sensitivity 64%; specificity 95%) (16).

Follow-up of CFLD with cirrhosis/portal hypertension

After diagnosis, follow-up of *CFLD with cirrhosis/portal hypertension* is essential to assess treatment efficacy and to prevent complications. Debray-Colombo recommend at least annual screening for portal hypertension complications such as esophageal varices, ascites, and signs of liver function deterioration or failure (1). Patients should be regularly screened for the development of hepatocellular carcinoma via alpha-fetoprotein levels and via ultrasound. A recent paper reported two cases of hepatopulmonary syndrome (HPS) in patients with CFLD (17). This complication might be suspected when oxygen saturation is lower in supine than in upright position (orthodeoxia). However, clinical symptoms of HPS can be masked in CF patients due to coexisting respiratory morbidity. Therefore, HPS is likely underdiagnosed in CF, and we propose to perform a contrast-enhanced echocardiogram if HPS is suspected.

Diagnosis of CFLI without cirrhosis/portal hypertension

CFLI *without* cirrhosis or portal hypertension refers to various other hepatobiliary changes frequently observed in CF patients. The challenge in the diagnosis of CFLI lies in distinguishing patients with hepatic changes that will progress to cirrhosis or portal hypertension from patients with hepatic changes that do not have a progressive clinical course. The rate of progression of many forms of CFLI to cirrhosis and portal hypertension has not (yet) been clearly established. Therefore, currently, all CF patients are screened for CFLI.

Physical examination aims at detecting hepatomegaly and splenomegaly. LFTs and ultrasound of the liver are currently recommended to assess CFLI (1). LFTs can reflect hepatocyte damage (transaminases), biliary tract pathology (GGT,

alkaline phosphatase (ALP) or synthetic dysfunction (albumin). LFTs are frequently increased in CF patients, either intermittently or persistently (18,19). Often the cause and clinical significance of elevated LFTs cannot be identified. Antibiotic usage and idiosyncratic reactions contribute to abnormal LFTs in CF (18). An isolated increase in transaminases may also suggest steatosis (1). Ultrasound of the liver is frequently abnormal in CF patients. Hepatomegaly with increased, homogeneous echogenicity is mostly due to steatosis, which may be caused by nutritional deficiencies or other unknown causes.

Le Maitre *et al.* recently highlighted the importance of magnetic resonance imaging (MRI) in assessing CFLI through visualization of the liver parenchyma and bile tract without contrast agents (14). In clinical practice, the use of MRI may be valuable but held back by high costs and extended examination times. TE and ARFI also play a role in detecting CFLI, aside from their role in identifying CFLD with portal hypertension. Studies assessing TE (12,13,15,20–23) and ARFI (15,21,24,25) have identified highly different cut-off values for the detection of CFLI. Both TE and ARFI seemed reliable for the exclusion of CFLI due to their high specificities (TE: 81-100%; ARFI: 90-94%), however, their sensitivities (TE: 43-92%; ARFI: 50-57%) were far from ideal in most studies. Altogether, TE and ARFI show potential to become implemented in CFLD screening, likely in combination with other tests. However, consensus needs to be reached concerning cut-off values for different age groups as well as on their value for individual patients. The studies discussed in the following sections made use of the Debray-Colombo criteria for CFLD diagnosis (1). Therefore, they include a heterogeneous group of CFLI, unless otherwise stated. The fibrosis serum markers tissue inhibitor of metalloproteinase-1 (TIMP-1) (adult population: sensitivity 63%; specificity 80%) and TIMP-2 (pediatric population: sensitivity 73%; specificity 72%) have also been tested for the diagnosis of CFLI (12). In this study, CFLI was diagnosed according to the Debray-Colombo criteria and therefore included a heterogeneous group of hepatic phenotypes. A recent study using serum proteome profiling identified TIMP-4 and Endoglin as possible serum markers for CFLI (20). Combining TIMP-4 or Endoglin with TE improved the sensitivity of TE, at the expense of specificity for CFLI diagnosis. As TE is a marker of liver stiffness, specifically diagnosing liver fibrosis was more successful with this combination of markers compared to using TIMPs alone. Altogether, these biomarkers show potential for early detection of CFLI; however, their availability is limited, validation studies are required, and costs may be a concern.

Whereas elevated LFTs in CF are nonspecific and therefore have limited value for the detection of identifying various types of CFLI, combination measurements that incorporate LFTs with other measurements (e.g. the APRI and Fibrotest) may be more valuable. The isolated value of APRI was suboptimal (adults: sensitivity 47-86%; specificity 71-96% (15,20,22); in children even lower (26)). This was likely due to the heterogeneity of types of CFLI included and high variability in used cut-off values among studies. Fibrotest, which combines alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, and ALT with patient age and gender, showed very low sensitivity (38%; specificity 90%) in one study (21) and better performance in another (sensitivity 82%; specificity 57%) (22). MicroRNAs (miRNAs) are involved in post-transcriptional regulation of gene expression. MiRNAs are tissue- and disease-specific and can be detected in serum (27). A recent study used the combination of serum miR-122, miR-21, and miR-25 for detecting liver involvement in CF, and found low sensitivity (47%) but a high specificity (94%) (28). These combinations of microRNAs were also able to distinguish mild from advanced fibrosis.

Follow-up of CFLI without cirrhosis/portal hypertension

While it is unclear to what extend CFLI actually increases the risk of developing cirrhosis or portal hypertension, annual follow-up visits should include screening for cirrhosis and portal hypertension. General tests for follow-up of liver involvement include a physical examination by a gastroenterologist, serum biochemical evaluation and abdominal ultrasound with CT or MRI in case of doubt (1).

Diagnosis of CF-related biliary tract abnormalities

Biliary tract disease is common in CF patients, even though it is usually asymptomatic. Biliary tract abnormalities include cholangiopathy, gallstones, neonatal cholestasis and gallbladder abnormalities such as a micro gallbladder (1,8). Cholangiopathy can be diagnosed by MRI, hepatobiliary scintigraphy, and magnetic resonance cholangiography (MRC), which shows findings similar to primary sclerosing cholangitis. Gallbladder abnormalities are diagnosed via ultrasound, MRI or MRC. Moreover, up to half of CF patients show intermittent GGT elevation (19). It is unclear whether these GGT elevations are related to biliary tract abnormalities. The clinical relevance of biliary tract abnormalities is unclear and tests to diagnose them are not routinely performed as part of CFLD screening.

Treatment

Treatment in CFLD should be aimed at prevention of portal hypertension and, if nevertheless present, on its treatment and prevention of complications. Unfortunately, current treatment options are limited and their potential to prevent portal hypertension has never convincingly been demonstrated. The complex pathophysiology, different phenotypical presentations and the lack of long-term studies certainly contributes to this phenomenon. Specific phenotypical presentations might require more targeted treatment. In the past few years, new treatments targeting liver diseases that show similarities in pathogenesis (e.g. primary biliary cholangitis (PBC)) have shown promising results in (pre)-clinical trials. Additionally, novel CFTR modulators targeting the underlying defect in CF may also prove to be of great importance in prevention or treatment of CFLD in the near future.

Ursodeoxycholic acid

Currently, ursodeoxycholic acid (UDCA) is the most commonly used drug for CFLD. UDCA increases hepatocellular and cholangiocellular secretion, thereby improving bile flow and reducing biliary toxicity (29). Additionally, it may increase bicarbonate secretion and has direct anti-inflammatory and anti-apoptotic effects in animal models (30,31).

The role of UDCA in CFLD treatment, however, remains controversial. In 2014 authors of a Cochrane Review concluded that there is insufficient evidence to justify the routine use of UDCA in CFLD on the basis of ten clinical trials (32). A recent paper argues that portal hypertension often precedes cirrhosis in CFLD, suggesting biliary cirrhosis might not be the leading pathophysiological mechanism for CFLD and thereby limiting the efficacy of UDCA (7). Other authors propose that the pathophysiology of CFLD relates more to inflammation than to cholestasis thereby also arguing against the usefulness of UDCA (6).

There is limited clinical evidence suggesting that UDCA improves liver biochemistry markers at moderate to high doses (33). A recent observational study showed minor improvement of liver stiffness in CFLD patients who started UDCA based on the Debray-Colombo criteria after one year of treatment (34). However, patient numbers were limited, and no improvements were observed in patients receiving UDCA for other reasons or patients with overt cirrhosis.

As stated above, the lack of studies on long-term effects of UDCA treatment constitutes a major drawback. Nevertheless, Debray-Colombo recommend starting treatment early after diagnosis with a relatively high dose of UDCA (20 mg/kg/day

in contrast to 10-15 mg/kg/day for PBC) (1). Concerns have been raised about long-term safety of these high UDCA dosages (35).

Taken together, short-term studies suggest that UDCA could improve serum LFTs, but it has remained unclear to what extend UDCA is able to change the natural course of CFLI and especially cirrhosis. Evidently, more studies investigating long-term effects and possible alternative treatments are needed.

Experimental treatments targeting bile acid metabolism

Recently, novel drugs that target bile acid receptors and metabolism to improve liver disease have gained more attention. Nor-UDCA is a synthetic homologue to UDCA which is currently under investigation for several liver diseases such as primary sclerosing cholangitis, PBC and non-alcoholic fatty liver disease. It has shown some promising results in pre-clinical studies (36). The supposed advantage of nor-UDCA over UDCA is that nor-UDCA mainly induces bile flow by increasing bicarbonate secretion. In contrast, UDCA increases bile flow by increasing bile acid secretion which may increase cellular toxicity. No data on the use of nor-UDCA in CF patients is currently available.

Obeticholic acid is a semi-synthetic bile acid analogue that functions as a potent farnesoid-X-receptor (FXR) agonist. It has been shown to improve outcomes in various liver diseases such as nonalcoholic steatohepatitis (37) and PBC (38). Activation of intestinal and hepatic FXR decreases hepatic bile acid synthesis and hepatobiliary toxicity in various cholestatic conditions. In this regard, FXR activation might be especially interesting for CF patients since hepatic bile acid synthesis is already increased due to intestinal bile acid malabsorption (39) Additionally, activation of FXR has anti-inflammatory effects which as mentioned previously, has been implicated in the pathophysiology of CFLD.

CFTR modulators

Major advances have been made in directly targeting CFTR to improve outcomes in CF. Ivacaftor (VX-770), a CFTR potentiator, improved pulmonary function of CF patients with specific CFTR gating mutations (40). More recently, a combination of ivacaftor with the CFTR corrector lumacaftor (Orkambi®) improved pulmonary outcomes in CF patients who are homozygous for the F508del mutation (41). Unfortunately, not much is known about the effects of CFTR modulators on CFLD. In the aforementioned studies, CF patients with abnormal liver function tests were excluded from participation. While during these trials elevated liver enzyme measurements were similar between ivacaftor/lumacaftor and ivacaftor treatment

versus placebo, more serious adverse events related to abnormal liver function tests have been observed with ivacaftor/lumacaftor treatment (41). This observation could indicate that these drugs have hepatotoxic side effects, even in the absence of overt CFLI or cirrhosis. One case report showed improvement of hepatic steatosis after two years of ivacaftor treatment (42).

Ivacaftor has been shown to improve extra-pulmonary parameters such as gastrointestinal function (43). However, this effect does not correlate well with the effect of ivacaftor on sweat chloride levels (a surrogate marker for CFTR function) or pulmonary function, suggesting a degree of organ specificity possibly due to other modifying factors (44). More studies are needed to determine whether CTFR modulators have a specific effect on CFLD.

Managing portal hypertension and liver transplantation

In patients where CFLD results in portal hypertension, various complications could arise including esophageal varices. Treatment options are determined on a case by case basis but include primary prophylaxis by either endoscopic variceal ligation or non-specific beta receptor blockade (e.g. propranolol) (1). However, the use of non-specific beta receptor blockade should be used with extreme caution in CF due to the potential of significant bronchoconstriction. One approach could be to perform a detailed pulmonary function test with and without non-specific beta receptor blockade, to assess the occurrence and severity of medication–induced bronchoconstriction. If life-threatening bleeding cannot satisfactorily be prevented by these treatments, either a portosystemic shunt or liver transplantation may become indicated. Liver transplantation may be combined with a lung and/or pancreas transplantation. However, combined liver-lung transplantation programs are only available in select centers due to the difficulty of the procedure and the high risk for complications. Unfortunately, there are limited publications regarding this matter and there is likely a publication bias (i.e. only successful case reports/series are published), making the estimation of success rate and complications difficult to assess. The timing and indication of liver transplantation for CF has been a matter of debate. Post-transplantation survival in CFLD patients is lower than in patients who received a liver transplantation for other indications (45). This decreased survival is likely due to an increased risk of other CF-related complications, such as CF-related diabetes in CFLD patients, and to pulmonary complications of CF. Making an extensive estimation of possible post-transplantation complications for each patient and considering a combined liver-(pancreas)-lung transplant is, therefore, warranted (46).

Conclusion

A combined European and North American initiative (ESPGHAN and NASPGHAN), has been initiated to reach a uniform definition and classification of CFLD, which will likely shape diagnostic criteria. In current clinical practice, the diagnosis of CFLD frequently is based on the Debray-Colombo criteria (1). A drawback of using these criteria is that varying phenotypical types of liver involvement are included and it is not always clear whether these are clinically relevant or play a role in development of cirrhosis or portal hypertension. Advances in understanding CFLD pathophysiology will likely guide the discovery of more phenotype-specific markers and treatments. It seems reasonable to assume that longitudinal rather than single measurements may become important for the diagnosis and follow-up of CFLD, as well as combinations of diagnostic tests rather than an isolated test or modality. Prospective studies are needed to validate the performance of the novel tests reviewed here. Yearly screening or follow-up for CFLD should include abdominal examination by a gastroenterologist, serum biochemical evaluation and abdominal ultrasound with, in case of doubt, follow-up by CT or MRI.

Current treatment options for CFLD are limited. UDCA does seem a relatively safe treatment (1), but its long-term efficacy and safety have not been demonstrated. Novel treatments for liver disease are being developed. Together with the implementation of CFTR modulators, these might prove to be beneficial for CFLD in the coming years.

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None

References of interest

*of special interest

**of outstanding interest

** (3) *Stonebraker JR, Ooi CY, Pace RG, Corvol H, Knowles MR, Durie PR, et al. Features of Severe Liver Disease With Portal hypertension in Patients with Cystic Fibrosis. Clin Gastroenterol Hepatol. 2016;14(8):1207–1215.e3.*

This study characterized the clinical features of severe CFLD and confirmed several risk factors (male gender, pancreatic insufficiency, early onset) and that LFTs are often near-normal in these patients.

** (4) *Koh C, Sakiani S, Surana P, Zhao X, Eccleston J, Kleiner DE, et al. Adult Onset Cystic Fibrosis Liver Disease: Diagnosis and characterization of an underappreciated entity. Hepatology. 2017 Apr;*

By following CF patients for up to 38 years, this study highlighted the occurrence of CFLD onset in adults, which was previously thought to be very rare. Additionally it proposed a adjusted version of the Debray-Colombo criteria inclusive of new diagnostic techniques.

* (16) *Bodewes FAJA, van der Doef HPJ, Houwen RHJ, Verkade HJ. Increase of serum γ-glutamyltransferase associated with development of cirrhotic cystic fibrosis liver disease. J Pediatr Gastroenterol Nutr 2015; 61: 113-118*

In this retrospective study, the authors looked at plasma γ-glutamyltransferase (GGT) levels, a routinely measured liver function test, in 277 pediatric patients who later developed CFLD with cirrhosis. They showed that in the period before developing overt clinical cirrhosis, multiple elevated GGT levels had potential to predict progression to cirrhosis in a 2-year period.

* (17) *Breuer O, Shteyer E, Wilschanski M, Perles Z, Cohen-Cymberknoh M, Kerem E, et al. Hepatopulmonary Syndrome in Patients With Cystic Fibrosis and Liver Disease. Chest. 2016 Feb;149(2):e35–8.*

This case report study of two patients with CFLD who developed hepatopulmonary syndrome aimed to raise awareness of this complication, which is probably underdiagnosed in patients with CFLD due to concomitant respiratory illness.

* (18) *Jong T, Geake J, Yerkovich S, Bell SC. Idiosyncratic reactions are the most common cause of abnormal liver function tests in patients with cystic fibrosis. Intern Med J. 2015;45(4):395–401.*

This paper explores the risk factors for abnormal LFTs in CF patients receiving antibiotics. It showed that antibiotics were often responsible for LFTs elevation and that antibiotic-induced liver injury was mostly idiosyncratic.

** (19) *Woodruff SA, Sontag MK, Accurso FJ, Sokol RJ, Narkewicz MR. Prevalence of elevated liver enzymes in children with cystic fibrosis diagnosed by newborn screen. J Cyst Fibros. 2017 Jan;16(1):139–45.*

This paper describes the (high) prevalence of abnormal LFTs in children with CF in a large population. This information is very valuable for the interpretation on LFTs in clinical trials with CF patients. Moreover, it highlights the importance of diagnostic criteria for CFLD, to avoid responding too aggressively to abnormal LFTs.

* (29) *Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: From UDCA to FXR, PXR and beyond. J Hepatol European Association for the Study of the Liver; 2015;62(S1):S25–37.*

Extensive review on new developments in regard to cholestatic liver diseases. It provides a clear description of the mechanisms of (novel) therapeutic strategies including UDCA, nor-UDCA and FXR modulation.

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