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## **Current Trends in Liver Biopsy Indications for Chronic Liver Diseases**

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Jean-François Cadranel and  
Jean-Baptiste Noursbaum

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### **1. Introduction**

At the present time, pathological examination of a liver fragment obtained by liver biopsy remains an essential diagnostic tool of numerous chronic liver diseases [1]. Indications for liver biopsy (LB) have changed considerably over recent years due to the development of sensitive and specific tests for diagnosis of several chronic liver diseases (i.e., serology for hepatitis C, antimitochondrial M2 in primary biliary cirrhosis, genetic screening for hereditary hemochromatosis), but also because of intensive development during the last decade of non-invasive assessment of fibrosis using serum tests (FibroTest®, FibroMeter®, APRI score) and/or by physical methods such as pulsed elastography (FibroScan®), in particular, for chronic hepatitis C. Ultrasound-guided liver biopsy is often necessary to obtain a tumor fragment in cases of suspected primary or secondary liver malignancy and will not be discussed here [1]. In the present article, we will limit ourselves to indications of liver biopsy in diffuse parenchymal disease of the liver and its relative and absolute contraindications. Modalities for performing liver biopsy and complications will not be discussed here. Liver biopsy is an invasive procedure with possible complications; thus, individual benefits for the patient must be weighed against possible risks. Liver biopsy is indicated when the expected amount of information obtained exceeds the risks related to the procedure, when the diagnosis required for establishing a prognosis cannot be obtained without pathological examination of the liver, and finally, when the treatment decision depends on pathological results [1].

2. Indications for LB

Indications for liver biopsy in chronic liver disease have evolved (Tables 1,2). The main advantages of LB with respect to the etiology of liver disease are shown in Table 2 and will be detailed later. The indication for liver biopsy is appropriate when the treatment or prognosis will be modified by results of histopathological examination of the liver. However, liver biopsy is not appropriate when the therapeutic decision and/or establishment of a diagnosis does not depend on histological findings [1].

Indications	
For diagnostic purposes	- Combination of several parenchymal liver diseases - Abnormal liver tests of unknown origin *. - Fever of unknown origin. - Focal or diffuse abnormalities on imaging studies.
For prognostic purposes	- Assessment of known parenchymal liver diseases.
For research purposes	- Development of treatments related to results of histological analysis

\* After complete check-up, according to (2)

Table 1. Indications for liver biopsy

Cause of liver disease	Diagnosis	Evaluation of fibrosis	Prognosis	Management
Hepatitis B	-	+++	+ (+)	+++
Hepatitis C	-	+++ (Non-invasive markers of fibrosis)	+ (+)	++++
Hemochromatosis	+/-	+++	+ (+)	+
Wilson's disease	++	+++	+	-
α-1 Antitrypsin deficiency	+	+++	Depends on lung status	+
Autoimmune hepatitis	+++	+++	+	++++
In particular, seronegative				
Primary biliary cirrhosis / overlap syndrome	++	+++	+++	++
Primary sclerosing cholangitis	++	+/0	0	+
Alcoholic liver disease	+/-	++	++	+
Severe acute alcoholic hepatitis	+++	NA	NA	+
Steatosis / steatohepatitis	+++	+++	+	+
Infiltrative lesions of the liver	++++	NA	NA	+
Medicinal cause	++	NA	NA	+
Follow-up after liver transplantation	++++	+++	+	+

NA: not applicable

Table 2. Utility of liver biopsy in clinical practice for diffuse parenchymal damage

<b>Etiology</b>	<b>1997 Study [31] of 2,084 biopsies (%)</b>	<b>2009 Study [13] of 8,580 biopsies (%)</b>
Hepatitis C	54.1	33.6
Delta hepatitis B	5.8	14.4
Hereditary hemochromatosis	4.3	1
Cholestatic disease of the liver (primary biliary cirrhosis, primary sclerosing cholangitis, chronic cholestasis)	4.3	3.7
Autoimmune hepatitis	1	3.5
Liver transplantation	3	12.
Miscellaneous	17.6	12.2
Metabolic steatopathy	unlisted	8.9

**Table 3.** Indications for liver biopsy. Evolutionary trend in France.

## 2.1. Chronic hepatitis C

Liver biopsy has long been the only reference for assessing necroinflammatory lesions and fibrosis in hepatitis C. Liver biopsy is most useful for evaluating the existence of co-morbidities: alcoholic liver disease, non alcoholic fatty liver disease and iron overload, which are especially common in patients with chronic hepatitis C. In 2002, the French consensus conference no longer recommended systematic liver biopsy in patients with consistently normal transaminases [2]. At that time, for patients recently contaminated with genotype 2 or 3 infection, without co-morbidity and/or when the indication was viral eradication independently of fibrosis data, then antiviral treatment could be undertaken without requiring LB [2]. Furthermore, liver biopsy is not useful when diagnosis of cirrhosis is obvious [2]. While abdominal ultrasonography is satisfactory for assessing the existence of steatosis, liver biopsy is needed in order to evaluate the existence of steatohepatitis, iron overload or alcoholic liver disease associated with hepatitis C. Such lesions are associated with more rapid fibrosis progression and a less favorable response to treatment. The major development over the last ten years, spurred by French teams, of non-invasive assessment of fibrosis during the course of hepatitis C has significantly reduced indications for liver biopsy in patients with chronic hepatitis C. Several serum tests (FibroTest®, FibroMeter®, Hepascore®) are currently being validated by the French High Authority of Health for establishing extent of fibrosis in patients with untreated chronic hepatitis C and no co-morbidity [3-5]. The FibroTest has been validated by numerous studies and several independent teams [6]. The FibroMeter® virus [9] has also been the subject of independent validations by different teams. FibroScan® is useful for confirming or ruling out the presence of cirrhosis [7, 8], and for patients with HIV-HCV co-infection. In a recent survey, the use of liver biopsy was reduced by 50 % for chronic hepatitis C patients [9]. Most hepatologists in France no longer recom-

mend first-line liver biopsy for chronic hepatitis C (Table 4). Discrepancy between results of serum fibrosis markers and FibroScan®, when performed simultaneously, is an indication for liver biopsy.

Transparietal liver biopsy	Transjugular liver biopsy
Absolute contraindications:	Hydatid cyst
Absence of patient cooperation	Cholangitis
Clotting abnormalities (see text)	Bile duct dilatation
Need to maintain anticoagulants or antiplatelets	Uncorrected hemostasis deficits
Vascular lesion along the puncture route	
Non-percussive or non-identifiable liver	
Hydatid cyst	
Suspicion of amyloidosis	
Relative contraindications	
Morbid obesity	
Ascites	
Infection of the right pleural cavity	

**Table 4.** Contraindications to transjugular and transparietal liver biopsy

**2.2. Hepatitis B and hepatitis B-delta**

Serum markers of non-invasive necroinflammatory lesions and fibrosis in hepatitis B and B-delta have not been fully validated, nor has the FibroScan [10, 11]. Scientific institutions recommend that liver biopsy be performed prior to any treatment decision in the context of chronic hepatitis B or B-delta. Liver biopsy is the best means of assessing necroinflammatory lesions and fibrosis in chronic hepatitis B [12]. The evolutionary trend in indications for liver biopsy for hepatitis C and B has been inverted over the last twelve years: the number of liver biopsies for hepatitis C in 2009 represented 33.6%, compared to 54.1% in 1997, this trend being related to development of non-invasive measures for assessing fibrosis; however, the number of liver biopsies for hepatitis B and delta-B has tripled in France [13] (Table 4). This is probably related to the increased number of patients with hepatitis B in France and the emergence of more effective treatment, along with insufficient validation of non-invasive fibrosis assessment methods.

**2.3. Alcoholic liver disease**

Liver biopsy remains essential in case of severe acute alcoholic hepatitis with Maddrey function above 32. In this situation, lesions of acute alcoholic hepatitis are absent in 20% of cases [14], while the benefit of corticosteroids in the absence of alcoholic hepatitis lesions has not been demonstrated with an increased risk of bacterial infection. However, this point has been debated by some authors [15]. When there are no signs of severe acute alcoholic hepatic

tis and if extensive fibrosis or cirrhosis is suspected, then the Fibrotest® [16] and FibroScan® [17] give satisfactory diagnostic performances.

#### 2.4. Non alcoholic fatty liver disease

In patients with hepatic steatosis as part of the metabolic syndrome, liver biopsy is useful for differentiating fatty lesions from steatohepatitis (NASH), the evolutionary potential of which is much more severe (risk of cirrhosis and hepatocellular carcinoma). The presence of body mass index > 30 kg/m<sup>2</sup>, AST/ALT ratio > 1, hypertriglyceridemia > 1.7 mmol/L, age > 50 years and a syndrome of insulin resistance are predictors of steatohepatitis and fibrotic lesions. When elements of metabolic syndrome exist with or without steatosis visualized on ultrasonography, then LB performed for what is referred to as “unexplained” cytolysis leads to a diagnosis of steatosis and steatohepatitis lesions in 60% of the cases [18]. Liver biopsy enables accurate diagnosis of lesions and evaluation of the degree of fibrosis [1]. It should be noted, however, that in this setting, steatosis FibroMeter® [19] and Fibromax® [20] can provide evidence of the existence of fibrosis and can predict the existence of NASH.

#### 2.5. Cholestatic liver diseases, and autoimmune diseases of the liver

Diagnosis of primary biliary cirrhosis is based on identification of cholestasis associated with antimitochondrial M2 antibodies. Liver biopsy is not useful for diagnosis of primary biliary cirrhosis [21], but is very useful for assessing the activity and extent of fibrotic lesions. FibroScan® in this indication can assess the presence or absence of cirrhosis [22]. Liver biopsy is useful in case of a poor response to ursodeoxycholic acid and/or in case of a drastic increase of transaminases. Liver biopsy is able to reveal moderate to severe lymphocytic piecemeal necrosis that may fit into the context of overlap syndrome, requiring a change in therapy and the addition of corticosteroids. During the course of autoimmune hepatitis [1, 23], liver biopsy is necessary to assess piecemeal necrotic lesions and fibrosis stage. It is especially helpful in the absence of antibodies. In autoimmune hepatitis, no method of non-invasive evaluation of fibrosis has been developed. Liver biopsy is also necessary prior to discontinuation of immunosuppressive therapy, since the presence of histological piecemeal necrotic lesions is associated with almost constant recurrence of outbreaks of cytolysis deleterious to the liver [24]. When confronted with possible chronic cholestasis, the diagnosis of primary sclerosing cholangitis is based on data from the magnetic resonance cholangiopancreatography (MRCP) [21]. Liver biopsy often confirms the diagnosis, but can appear normal in 25% of the cases. When MRCP is normal, liver biopsy enables diagnosis of cholangitis of small bile ducts and, in all cases, helps to clarify lesions due to hepatic fibrosis [1, 21].

#### 2.6. Genetic hemochromatosis

Diagnosis of hereditary HFE-gene-related hemochromatosis is based on the association of hyperferritinemia with elevated saturation of transferrin and presence of the C282Y mutation in the homozygous state. Thus, liver biopsy is not mandatory for diagnosis. It is still indicated, however, when serum ferritin is higher than 1,000 µg/L, and/or when the AST are increased and/or if hepatomegaly is present [25]. Simple markers (platelet count and



transaminases, possibly combined with the dosage of hyaluronic acid and/or use of FibroScan) can indicate the existence or absence of extensive fibrosis and help to guide indications for liver biopsy.

## 2.7. Unexplained abnormal liver tests

Liver biopsy is often proposed in case of unexplained abnormal liver tests, when physical examination, biochemical and serological tests, imaging investigation could not establish a diagnosis. In one study including 354 patients, non alcoholic fatty liver disease was the definite diagnosis in 64 % of the cases. Other lesions included drug induced liver injury, alcohol-related liver disease, auto-immune hepatitis, primary sclerosing cholangitis, primary and secondary biliary cirrhosis, hemochromatosis, amyloid and glycogen storage disease, and cryptogenic hepatitis [26]. In another study including 272 patients, NAFLD represented 59.5 % of the cases [18].

## 2.8. Other indications (Table 3)

Liver biopsy is essential for the diagnosis of rare diseases of the liver such as Wilson's disease, wherein the hepatic copper concentration has to be measured, a deficiency in alpha-1 antitrypsin with evidence of PAS-positive cells, overload diseases such as Gaucher's disease, and amyloidosis, when there exists no other alternative [2]. In case of amyloidosis, liver biopsy should be performed via the transjugular route, since there is a major risk of bleeding in case of LBP performed via the transparietal route. Liver biopsy also helps in diagnosing rare diseases (nodular regenerative hyperplasia, congenital hepatic fibrosis) in case of prolonged abnormal liver function tests [1]. In case of severe acute hepatitis, emergency liver biopsy performed via the transjugular route may be particularly useful for diagnosing seronegative autoimmune hepatitis, infiltrative lesions of the liver, hepatitis or herpes [1]. Liver biopsy is essential for diagnosis of abnormalities in liver function tests when monitoring patients after liver transplantation in order to give a positive differential diagnosis of the following anomalies: rejection, infection, drug-induced liver injury, bile duct injury and viral reinfection. In case of hepatitis C virus recurrence in the liver transplant, liver biopsy is indicated; however, the FibroScan® is currently being assessed for evaluating damage from hepatic fibrosis. In case of suspected drug-induced hepatitis, liver biopsy may be useful if biochemical abnormalities persist beyond 3 months after cessation of treatment or if there is evidence suggesting injury to the bile ducts, such as a prolonged cholestatic syndrome.

It is essential that the pathologist be provided with relevant and complete clinical and biological information. Such information should be available before performing liver biopsy in suspected cases of rare diseases of the liver, or when bacteriological seeding or special staining has to be performed [1], so that the fresh liver fragment is immediately transmitted to the pathology or microbiology laboratory.

### 3. Limitations

Liver biopsy has remained the “gold standard” for years. However, it is imperfect since a large biopsy is required to make an accurate assessment of fibrotic stage and inflammatory grade. Pathologists estimated that a 25 mm-long fragment obtained with a 16-G needle was necessary to accurately determine the grade of chronic liver disease [27]. Colloredo et al. showed that eleven to fifteen complete portal tracts was the minimal number below which disease stage was significantly underestimated [28]. In a large review of the literature including 10,027 LB, Cholongitas et al. showed that the mean  $\pm$  SD length was 17.7 $\pm$ 5.8 mm and the mean  $\pm$  SD number of portal tract was 7.5 $\pm$ 5.8 [29]. This implies that at least two passes would be necessary to obtain a 2.5 cm long specimen, thus potentially increasing the risk of complications.

### 4. Optimal methods for carrying out lb in 2012

Methods for performing LB will not be detailed here, but are available in practical guidelines [30]. Several issues will be addressed:

When all conditions are met, then “ambulatory” liver biopsy may be performed [30]. In the study published in 2000 (completed in 1997) [31], 27% of liver biopsies were performed on an outpatient basis, most often for chronic hepatitis C; this figure is currently at 45% [13]. Several French teams have shown that outpatient liver biopsy is a safe and effective procedure and that liver biopsy performed on an outpatient basis reduces discomfort and increases the acceptability of subsequent examination conducted under the same conditions. If all conditions are not met and/or if organizational arrangements do not permit it, then liver biopsy should be performed via traditional hospitalization.

LB is carried out by hepatogastroenterologists, radiologists and occasionally by surgeons. Currently, liver biopsy is performed in France by a hepatogastroenterologist in 63.5% of cases, by a radiologist in 34.8% of cases and by a surgeon in 1.7% of cases [13]. The increasing number of liver biopsies performed by radiologists in France is linked to an increased number of biopsies performed using ultrasound guidance or guided real-time ultrasonography [30] and by the development of the transvenous route as compared to the transparietal route. Indeed, in 1997, 9% of liver biopsies were performed via the transvenous route compared to 22.4% in 2009 [13]. In the US, 50% of biopsies are performed by radiologists. In that country, it is felt that the number of LB performed in order to gain sufficient expertise is at least 40, carried out in the presence of an experienced radiologist [1].

### 5. Absolute and relative contraindications for LB

Absolute and relative contraindications for LB depend on the surgical approach recommended. Contraindications for liver biopsy using the transjugular or transparietal route [1, 30] are summarized in Table 4.



### 5.1. Lack of patient cooperation

Absence of patient cooperation is an absolute contraindication for transparietal LB. Indeed, in case of uncontrolled respiratory movements or agitation of the patient, the biopsy needle may cause a tear in the liver capsule, bleeding or a pneumothorax. If the patient is unable to maintain breath holding, or in the absence of expected cooperation, the question of the appropriateness of the indication for liver biopsy must be raised. If this indication is maintained, then liver biopsy under general anesthesia might be necessary, eventually via the transvenous route.

### 5.2. Hemostasis disorders, history of unexplained bleeding, hemostatic disease

It is recommended that transparietal liver biopsy should not be performed if the prothrombin rate is less than 50%, the platelet count is below 50 Giga/L or 60 Giga/L, if activated partial thromboplastine time is greater than 1.5-fold that of the control or when bleeding time is lengthened. The need for maintaining an anticoagulant or an antiplatelet is also a contraindication to transparietal LB. Likewise, the existence along the puncture route of a hemangioma or a vascular tumor is a contraindication for liver biopsy without real-time guidance. In this case, ultrasound-guided liver biopsy may eventually be used [1]. For patients with hemophilia, transvenous liver biopsy can be performed safely after correction of anomalies. In this indication, non-invasive blood markers of fibrosis and FibroScan® are particularly useful.

### 5.3. Impossibility of carrying out liver detection

The incapacity to detect the liver by percussion or ultrasound is an absolute contraindication to performing transparietal liver biopsy, as is suspicion of hydatid cyst.

### 5.4. Dilatation of extrahepatic or cholangitic bile ducts

Dilatation of the extrahepatic bile ducts and cholangitis are contraindications to transparietal liver biopsy [1].

### 5.5. Relative contraindications

Morbid obesity, severe ascites persisting after evacuation and infection of the right pleural cavity are contraindications for transparietal liver biopsy [1]. The transvenous route can be used in all these settings, and especially in case of significant ascites, morbid obesity, vascular liver, anticoagulant or antiplatelet treatment that cannot be stopped, hemodialysis, chronic renal failure or suspicion of amyloidosis when liver biopsy is necessary. Contraindications for the transvenous route include bacterial cholangitis, hydatid cyst and uncorrected deficits in hemostasis [1, 30].

## 6. Reducing the risk of complications

Compliance with absolute and relative contraindications for liver biopsy should lead to a decrease in serious accidents due to LB, the presentation of which is beyond the scope of this

paper. Liver biopsy is an invasive procedure with the possible risk of severe complications, approximately 0.5/1,000 [1, 30]. Liver biopsy is a procedure for which there exists residual mortality [32]. Although serious complications have decreased over time, mortality after performing transparietal liver biopsy remains at 0.2% and deaths related to liver biopsy for diffuse parenchymal liver amount to 1 out of 10,000 LB [32]. This risk, however, has decreased dramatically over time because of improvement in indications for liver biopsy and compliance with contraindications [32].

## 7. Conclusion

Liver biopsy remains useful for making an etiological diagnosis and a prognostic evaluation of many non-viral liver diseases, particularly in the context of autoimmune liver diseases, as well as for monitoring liver transplant patients. Liver biopsy is of great value in cases of several associated parenchymal diseases, so as to determine the extent of each, especially in hepatitis C. However, within the setting of isolated hepatitis C without co-morbidity, we feel that first-line LB is no longer appropriate.

The authors declare that they have no conflicts of interest.

## Author details

Jean-François Cadranel<sup>1</sup> and Jean-Baptiste Noursbaum<sup>2</sup>

1 Service d'Hépatogastroentérologie et de Nutrition, Centre Hospitalier Laënnec, France

2 Service d'Hépatogastroentérologie, Hôpital de la Cavale Blanche, Brest, France

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