For hepatologists, liver biopsy is considered an essential procedure to aid in making rational decisions. For patients and general practitioners, it may be considered an aggressive procedure. Therefore, there is a risk that treatment will be reduced in frequently occurring diseases such as chronic hepatitis C, where liver biopsy is considered mandatory for making treatment decisions.

This review aims to discuss the appropriateness of liver biopsy in two frequent liver diseases: hepatitis C and alcoholic liver disease.

The authors conclude that liver biopsy is used extensively, but its appropriateness has not been evaluated perfectly. Therefore, further evaluation of the appropriateness of liver biopsy in the practical algorithm of such diseases is needed.

Key Words: Alcoholic liver disease; Hepatitis C; Liver biopsy; Liver biopsy appropriateness
THE EVALUATION OF LIVER BIOPSY APPROPRIATENESS IN THE REAL WORLD

When the appropriateness is controversial among experts, there is certainly a place for evaluation.

In the real world, there are probably some clinical situations where the appropriateness or nonappropriateness is so obvious that the evaluation is inappropriate.

From a clinical point of view, biopsy is appropriate when a therapeutic decision or a diagnostic decision depends on the liver histology. Biopsy is not appropriate when there is no therapeutic decision or diagnostic decision that depends on the liver histology.

Concordance among pathologists, techniques and sampling errors: Several chronic liver disease studies have evaluated the intra- and intenobserver (pathologist) concordance (8-11), the discordances among methods (12-16) and the sampling errors (8,17). For both alcoholic and viral chronic liver disease, there were significant concordance values for standardized items, particularly for fibrosis staging (9-12).

Four randomized trials compared different biopsy methods (13-16). For the diagnosis of cirrhosis, one trial observed better sensitivity of laparoscopy versus percutaneous biopsy (13), and another trial observed a better sensitivity of the Tru-Cut (Tru-Cut, London, United Kingdom) versus the Menghini needle (14). One trial observed larger sampling and fewer adverse events with the ultrasound-guided, anterior, large bore cutting needle biopsy than with the intercostal Menghini technique (15). Another trial observed fewer adverse events when ultrasound-guided biopsy was used (2% versus 9%; P<0.05) no matter which needle was used (16).

Few studies have assessed the sampling variability. When three percutaneous biopsies were performed in 75 patients through a single entry site, the overall concordance rate was only 51% (17). When laparoscopic biopsy from the right lobe was compared with biopsy of the left lobe in 80 alcoholic patients, the overall concordance rate was 70%, including 73% for the staging of fibrosis (12).

Recently, the standards of a normal liver were revisited (18-19) because no scoring system had integrated a definition of normal liver structure in its own definition.

ADVERSE EVENTS AND MORTALITY OF LIVER BIOPSY

Published articles (with more than 200 patients) assessing severe adverse events and mortality rates are summarized in Table 1 (20-28). There was a significant heterogeneity among the observed mortality rates for biopsy, ranging from 0 to 0.33 deaths per 1000 biopsies. Risk factors identified were older age and cirrhosis.
APPROPRIATENESS OF LIVER BIOPSY IN
ALCOHOLIC LIVER DISEASE

Extremely simple view: In alcoholic liver disease, biopsy can be viewed as inappropriate when alcohol consumption is elevated and liver tests are abnormal. Whatever the biopsy’s result, the clinical decision will be to recommend alcohol abstinence.

Intermediate point of view: In fact, things are more complicated, and biopsy can be appropriate for making therapeutic decisions. In patients with alcoholism and severe liver disease, biopsy is necessary in order to decide whether corticosteroid treatment is necessary. Seventy per cent of patients with alcoholism with severe liver disease have acute alcoholic hepatitis (MADDREY index higher than 32 – that is patients with jaundice and severe impairment of prothrombin time). Randomized trials have shown that 28 days of corticosteroid treatment improves the survival of patients with acute alcoholic hepatitis (29-31).

Biopsy may be viewed as necessary for the diagnosis of cirrhosis, which requires a different follow-up than non-cirrhotic diagnoses. In patients without cirrhosis, it is not necessary to screen for varices or hepatocellular carcinoma.

When cirrhosis is obvious in a patient with alcoholism and without severe liver disease, biopsy is not appropriate to justify the diagnosis of alcoholic hepatitis. Even if this statement seems logical, there are few studies in the literature estimating the ‘obviousness’ of cirrhosis. The following signs have potentially high positive predictive values: firm liver, ascites, splenomegaly, spider angioma, prothrombin time lower than 60%, low serum apolipoprotein-AI concentration, high serum hyaluronate and platelet count below 100,000 per mm$^3$.

A reduction in the indications for biopsy in heavy drinkers may be achieved by increasing the positive predictive value and the negative predictive value of cirrhosis markers.

### Table 1

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Number of patients</th>
<th>Type of biopsy</th>
<th>Design</th>
<th>Adverse events definition</th>
<th>Severe adverse events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gayral et al, 1979 (20)</td>
<td>2346</td>
<td>Laparoscopy, percutaneous, surgery</td>
<td>Retrospective</td>
<td>Bleeding</td>
<td>11 4.7 2.3-8.4</td>
<td>4 1.7 0.5-4.4</td>
</tr>
<tr>
<td>Lebrec et al, 1982 (21)</td>
<td>932</td>
<td>Transvenous</td>
<td>Retrospective</td>
<td>Bleeding</td>
<td>1 1.1 0.3-6.0</td>
<td>1 1.1 0.3-6.0</td>
</tr>
<tr>
<td>Piccinino et al, 1986 (22)</td>
<td>68,276</td>
<td>Intercostal</td>
<td>Retrospective</td>
<td>Bleeding, pneumothorax, biliary peritonitis</td>
<td>137 2.0 1.7-2.4 5 0.07 0.02-0.017</td>
<td></td>
</tr>
<tr>
<td>McGill et al, 1990 (23)</td>
<td>9212</td>
<td>Percutaneous</td>
<td>Retrospective</td>
<td>Bleeding</td>
<td>22 2.4 1.5-3.6 10 1.1 0.5-2.0</td>
<td></td>
</tr>
<tr>
<td>Maharaj et al, 1992 (24)</td>
<td>2646</td>
<td>Percutaneous</td>
<td>Prospective</td>
<td>Bleeding, pneumothorax, biliary peritonitis, pain</td>
<td>63 24 18-30 8 3.0 1.3-5.9</td>
<td></td>
</tr>
<tr>
<td>Van Thiel et al, 1993 (25)</td>
<td>12,750</td>
<td>Percutaneous transplant centre</td>
<td>Retrospective</td>
<td>‘Major complications’</td>
<td>26 2.0 1.3-3.0 0 0.0 0.0-0.3</td>
<td></td>
</tr>
<tr>
<td>Janes et al, 1993 (26)</td>
<td>405</td>
<td>Percutaneous</td>
<td>Retrospective</td>
<td>Admission</td>
<td>13 32 17-54 0 0.0 0.0-9.1</td>
<td></td>
</tr>
<tr>
<td>Gilmore et al, 1995 (27)</td>
<td>1500</td>
<td>Percutaneous</td>
<td>Retrospective</td>
<td>Bleeding</td>
<td>26 17 11-25 5 3.3 1.1-7.8</td>
<td></td>
</tr>
<tr>
<td>Vivas et al, 1998 (28)</td>
<td>378</td>
<td>Percutaneous</td>
<td>Prospective</td>
<td>Admissions and bleeding</td>
<td>7 19 7-38 0 0.0 0.0-9.7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>98,445</td>
<td></td>
<td></td>
<td></td>
<td>306 3.1 2.8-3.5 33 0.3 0.2-0.5</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** Ranges of sensitivity and specificity of cirrhosis markers in heavy drinkers. Alcoholic cirrhosis: ranges of sensitivity and specificity of PGA Prothrombin gamma glutamyl transpeptidase apolipoprotein-AI; P-III-P Procollagen III peptide. Prothrombin, hyaluronic acid receiver operating characteristic curves. Data from references 30-35
Cirrhosis markers in heavy drinkers (32-35) are summarized in Figure 2.

**Extremely complicated view:** Acute alcoholic hepatitis exemplifies the complexity of appropriateness of evaluation.

The first difficulty is the possible variability of the histological definition because alcoholic hepatitis can be defined as the presence of hyalin necrosis, Mallory bodies and polymuclear infiltrate. Most often the presence of two features among these lesions is necessary, but this has not been validated.

The second difficulty is whether corticosteroids are recognized as an effective treatment of severe alcoholic hepatitis. There is a long history of corticosteroid efficacy evaluation. Since 1971, 13 randomized, clinical trials and six meta-analyses have been performed. The results among trials were discordant. Among the meta-analyses, there was only one that was not affected significantly by corticosteroids (36). In this meta-analysis, trials were weighted and the trial with the biggest weighting factor was the trial by Mendenhall et al (37). Unfortunately this trial was very different from others because 50% of patients did not have severe hepatitis and 68% did not have biopsy. Furthermore, the dose of corticosteroid used in the trial was lower than usual, with a decreasing regimen. The mean dose was 23 mg/day of prednisolone versus 40 mg in the other trial. Finally, after excluding the patients without severe diseases, the authors observed a significant effect with corticosteroids. After evaluating these different factors, it was concluded that liver biopsy is appropriate.

**APPROPRIateness OF LIVER BIOPSY IN CHRONIC HEPATITIS C**

**Extremely simple view:** In patients with chronic hepatitis C, liver biopsy may be considered inappropriate if the patient is hepatitis C-positive by polymerase chain reaction (PCR) and has abnormal serum transaminase levels. The indication of treatment by combination ribavirin and interferon, which has a 40% mean sustained response rate, may be considered mandatory.

**Intermediate point of view:** Recent consensus conferences have stated that liver biopsy is mandatory in patients with chronic hepatitis C with abnormal alanine aminotransferase (ALT) levels, permitting grading and staging of the disease (1,38). It has been stated that liver biopsy should be performed before initiating treatment and that it is not known whether and when repeat biopsy is necessary.

Liver biopsy can assess the rate of disease progression when the date of contamination is known (fibrosis progression rate) and to improve the prediction of treatment response.

For diagnostic decisions, as discussed for alcoholic liver disease, biopsy may be viewed as necessary in order to diagnose cirrhosis, which may imply a different follow-up than in non-cirrhotic patients. In a patient with cirrhosis, it is necessary to screen for varices and hepatocellular carcinoma. When the cirrhosis is obvious in a patient with hepatitis C, biopsy is not appropriate. For patients with alcoholic liver disease, few studies have estimated the predictive values of clinical, biological (39-40) or morphological signs (41-42). The following signs have potentially high positive predictive values: firm liver, ascites, splenomegaly, spider angiomata, prothrombin time lower than 60%, high serum hyaluronate levels and platelet counts below 100,000 per mm$^3$. With ultrasound, liver surface nodularity and reduction of portal flow velocity have better predictive values. A reduction of biopsy indication may be achieved by increasing the positive predictive value and the negative predictive value of cirrhosis markers. Cirrhosis markers in chronic hepatitis C are summarized in Figure 3.

**Extremely complicated view:** In patients with hepatitis C, the indication of liver biopsy is complicated. In patients with acute hepatitis C, because of the effectiveness of treatment and the high (80%) spontaneous evolution to a chronic disease, treatment seems mandatory. In chronic hepatitis C, liver biopsy is probably not mandatory in patients who can contaminate other people or in patients who have extrahepatic manifestations impairing quality of life. The issue is that the definition of these groups is complicated. It seems reasonable to consider that a cardiac surgeon who is hepatitis C-positive by PCR is at risk of contaminating patients, but what about a nurse in a psychiatric ward? Should prostitutes be considered at risk of contaminating clients? Is an active intravenous drug user considered at risk of contaminating other intravenous drugs users? Another difficult issue is the definition of extrahepatic manifestations impairing quality of life and related to hepatitis C virus infection. In a cohort of 1614 patients (43), at least one clinical extrahepatic manifestation was observed in 1202 patients (74%; 95% CI 72 to 77). Five manifestations had a prevalence above 10%, including arthralgia (23%), paresthesia (17%), myalgia (15%), pruritus (15%) and sicca syndrome (11%). If treatment is effective for these symptoms, liver biopsy is not mandatory. Studies need to be performed to estimate which percentage of...
these symptoms are due to hepatitis C virus infection and what the efficacy of hepatitis C treatment is.

Another issue is the diagnosis of minimal disease without biopsy. Among patients who are hepatitis C-positive by PCR with sustained, normal transaminase levels, despite a low median fibrosis progression rate, only 20% have a normal liver (no activity and no fibrosis) (44). Thirteen per cent of patients have extensive fibrosis (META VIR stage 2, 3 or 4), for which treatment is mandatory. No markers exist to exclude patients with minimal disease.

One last common issue is the influence of other risk factors such as alcohol consumption. A liver biopsy may be considered appropriate in patients with hepatitis C who consume more than four drinks per day to differentiate the lesions related to alcohol or the virus.

CONCLUSIONS
Liver biopsy is used extensively, but its appropriateness has not been evaluated perfectly. Liver biopsy is appropriate for few diagnoses, and many stagings of chronic liver diseases such as alcoholic liver disease and chronic HCV. However, the appropriateness of liver biopsy in the practical algorithm of such diseases should be further evaluated. An excess use of liver biopsy, because of its cost and risk, may be a barrier to treatment. Underused liver biopsy may lead to inappropriate treatment of hepatitis.

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