Liver Biopsy

Don C. Rockey,[1] Stephen H. Caldwell,[2] Zachary D. Goodman,[3] Rendon C. Nelson,[4] and Alastair D. Smith[5]

This position paper has been approved by the AASLD and represents the position of the association.

Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1]; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines[2]; and (4) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart Association Practice Guidelines[3]).[4]

Introduction

Histological assessment of the liver, and thus, liver biopsy, is a cornerstone in the evaluation and management of patients with liver disease and has long been considered to be an integral component of the clinician's diagnostic armamentarium. Although sensitive and relatively accurate blood tests used to detect and diagnose liver disease have now become widely available, it is likely that liver biopsy will remain a valuable diagnostic tool. Although histological evaluation of the liver has become important in assessing prognosis and in tailoring treatment, noninvasive techniques (i.e., imaging, blood tests) may replace use of liver histology in this setting, particularly with regard to assessment of the severity of liver fibrosis.[5,6] Several techniques may be used to obtain liver tissue; a table including/defining specific terms has been provided in an effort to standardize terminology (Table 2). All liver biopsy techniques require specific training so as to ensure appropriate-sized specimen retrieval and the lowest rate of complications. Although liver biopsy is often essential in the management of patients with liver disease, physicians and patients may find it to be a difficult undertaking because of the associated risks. The purpose of this practice guideline is to summarize the current practice of liver biopsy and make recommendations about its performance. This guideline deals exclusively with liver biopsy as it relates to adult liver disease.

Indications for Liver Biopsy—Overview

Historically, liver biopsy was used almost exclusively as a diagnostic tool.[7,8] However, as the result not only of new natural history data and the introduction of many new therapies for patients with liver disease, liver biopsy and histological assessment of the liver has now taken on an important role in clinical management. Therefore, as of 2009, liver biopsy currently has three major roles: (1) for diagnosis, (2) for assessment of prognosis (disease staging), and/or (3) to assist in making therapeutic management decisions.

Diagnosis. For many diseases, clinical and/or blood-based tests suffice to establish a diagnosis (typical examples include hepatitis B [HBV] or hepatitis C virus [HCV] infection). Nonetheless, liver biopsy is often a

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; ANA, antinuclear antibody; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; IgG, immunoglobulin G; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PT, prothrombin time; US, ultrasound.

From the [1]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX; [2]Gastroenterology Division, University of Virginia, Charlottesville, VA; [3]Armed Forces Institute of Pathology, Washington, DC; [4]Department of Radiology and [5]Gastroenterology Division, Department of Medicine, Duke University Medical Center, Durham, NC.

Received November 12, 2008; accepted November 13, 2008.

Address reprint requests to: Don C. Rockey, M.D., Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8887. E-mail: don.rockey@utsouthwestern.edu; fax: 214-648-0274.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22742

Potential conflict of interest: Nothing to report.

Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

critical component in establishing the diagnosis of many (other) forms of liver disease. Although histological assessment alone may be able to make a diagnosis on occasion (i.e., a florid duct lesion in primary biliary cirrhosis [PBC]), liver histology is typically and most appropriately considered in conjunction with the full gamut of clinical and laboratory data. Acute and chronic hepatitis, cholestatic disorders, fatty liver disease, vascular diseases, infiltrative or storage diseases, some infectious and granulomatous diseases, and other disorders may be associated with characteristic histological abnormalities that are helpful in diagnosis.[9] Liver biopsy is particularly useful in patients with atypical clinical features. For example, liver histology can help distinguish between autoimmune hepatitis (AIH) and nonalcoholic fatty liver disease (NAFLD) in an obese patient with elevated levels of alanine aminotransferase (ALT), raised immunoglobulin G concentration (IgG), and/or a positive antinuclear antibody (ANA) titer. Liver histology may also be very helpful in patients with coexisting disorders such as steatosis and HCV or hemochromatosis[10,11] or an "overlap" syndrome of PBC with AIH.[12]

Table 2. Liver Biopsy Terminology

Term	Definition
Liver biopsy	Any type of liver biopsy
Transthoracic palpation/percussion-guided	The most appropriate biopsy site is guided transcutaneous determined on the basis of clinical examination. Traditionally used in practice.
Transthoracic, image-guided	The most appropriate biopsy site is determined or confirmed usually by ultrasound (US) imaging before the biopsy
Transthoracic, real-time image-guided	The most appropriate biopsy site is determined by US (or CT) imaging. Image guidance is used in real-time for tissue procurement
Subcostal, real-time image-guided	This biopsy is accomplished in almost identical fashion as above, except that the approach is subcostal rather than transthoracic
Transvenous or transjugular	Biopsy is accomplished through a jugular or femoral venous approach under fluoroscopic guidance

It is likely that liver biopsy will always play a role in the management of the patient with a diagnostic dilemma. This includes the patient with abnormal liver tests of unknown etiology (see below) or the patient in whom a specific liver disease has been considered, but has not yet been confirmed. Examples include patients with a variety of possible diseases, including, but not limited to hereditary disorders such as Wilson disease, alpha-1-antitrypsin disease, glycogen storage diseases, tyrosinemia, Niemann-Pick disease, amyloidosis, and others.[13-26] Liver histology may also be helpful diagnostically in patients with apparent systemic diseases in which the liver appears to be involved. Microscopic examination of the liver in patients with suspected hereditary hemorrhagic telangiectasia is rarely necessary, and should probably be performed via the transvenous route, concomitant with measurement of the portosystemic pressure gradient.[15] Liver histology may provide important diagnostic information in patients with acute liver failure (ALF).[27] For example, liver biopsy is helpful in making a specific diagnosis in specific settings (e.g., herpes virus infection, Wilson disease, AIH, and malignancy),[27,28] which in turn may guide more specific therapy.

Liver histology in patients with hepatomegaly or apparent diffuse disease may help establish a diagnosis, but whether it is clinically useful or cost effective is unknown. Examples of diffuse diseases include amyloidosis,[29,30] granulomatous hepatitis caused by any of a number of processes, and a host of other miscellaneous disorders.

Prognosis. A further important use of liver biopsy is in assessing disease severity, notably fibrosis, which, as a precursor to cirrhosis, may predict the emergence of complications of portal hypertension and also liver-related morbidity and mortality. Evidence in the area of HCV emphasizes the role of fibrosis assessment in determining

prognosis. For example, alcohol consumption, increased hepatic iron concentration, and/or hepatic steatosis, all of which are associated with more rapid fibrosis progression in patients with chronic HCV,[10,31-33] are currently assessed best by histology.[34] Further, specific evidence links fibrosis and prognosis; an example of this logical relationship is that in patients with HCV infection after liver transplantation, mortality was increased in those with advanced compared to minimal fibrosis.[35] Also, progression of NAFLD and eventual liver-related mortality appear to be related to the initial fibrosis stage.[36] Evidence that fibrosis assessment is important in prognosis also exists in PBC; in a long-term cohort study of 160 patients with PBC, for every stage increase of fibrosis identified (on a 1-4 point fibrosis scale) on initial liver biopsy, there was a twofold increase in future complications or death (relative risk 2.4; 95% confidence interval [CI]: 1.6-3.6).[37] In cases of genetic hemochromatosis, survival in patients without cirrhosis is similar to the normal control population, while mortality in those with advanced fibrosis/cirrhosis is significantly increased[38] and patients with cirrhosis are at increased risk of hepatocellular cancer (HCC),[38] and should be screened. Liver histology in patients with AIH may also provide prognostic information; the overall outcome for those with cirrhosis appears to be poorer than that for those without cirrhosis.[39] Finally, patients with fibrosis regression may actually be protected from developing clinical complications.[40] Thus, accurate assessment of liver fibrosis by histological analysis clearly provides important prognostic information.

Assessment of liver histology may be particularly beneficial in patients with human immunodeficiency virus and HCV who have persistently normal ALT levels, because these patients may have significant fibrosis, which may be of prognostic importance. This allows the clinician to determine the extent of liver fibrosis and, consequently, to assess suitability for treatment.[41]

Treatment. Currently, liver biopsy is used more than ever to develop treatment strategies. As previously emphasized, this has evolved because of the many new therapies available for patients with a variety of liver diseases. Not only can a treatment plan be instituted in a patient after a specific diagnosis is made (i.e., steroids in the setting of AIH), but among those with established liver disease, treatment may be predicated on the specific histological lesion. In the latter circumstance, therapy is usually directed at the patient with a more advanced histological stage. For example, histological analysis of the liver in patients with HCV provides information about the grade (degree of inflammation), which in turn presumably reflects to what extent the liver disease injury remains ongoing. In patients with chronic HCV-induced liver disease, treatment is often advocated for those with at least moderate to severe stages of fibrosis, but may be withheld when fibrosis is minimal or absent.[42] Liver histology is also commonly used in disease monitoring of patients with AIH. First, the portal plasma cell score (a measure of portal-based plasma cell infiltrate) may predict relapse,[43] and second, liver biopsy is often obtained prior to steroid dose reduction and/or discontinuation of immunosuppressive therapy altogether because the incidence of relapse is substantial in patients with evidence of residual interface hepatitis.[44] Finally, there is evidence that patients with PBC with advanced fibrosis at diagnosis may respond less well to ursodeoxycholic acid than do patients with minimal or mild fibrosis, thus placing them at risk of more rapid disease progression and premature death/requirement for liver transplantation.[45]

For further information on the role of histological analysis in the management of individual liver diseases, please see guidelines for HCV,[46] HBV,[47] hemochromatosis,[48] PBC,[49] AIH,[44] and Wilson disease.[50]

Table 3. Indications for Liver Biopsy

Diagnosis
Multiple parenchymal liver diseases
Abnormal liver tests of unknown etiology
Fever of unknown origin
Focal or diffuse abnormalities on imaging studies
Prognosis—Staging of known parenchymal liver disease
Management—Developing treatment plans based on histologic analysis

For more information on specific liver diseases, see Table 4

Use of Liver Biopsy in Specific Diseases

The diseases and situations in which liver biopsy may be indicated are listed in Tables 3 and 4. It is important to emphasize that the role of histological analysis of the liver in the management of patients with liver disease is likely to evolve over time, particularly as noninvasive modalities for assessment of fibrosis (and perhaps inflammation) are positioned more in the mainstream.[5,6] Further information on the role of liver biopsy and histological analysis in specific liver diseases is highlighted below and in published AASLD guidelines referred to above.[44,46-49]

Abnormal Liver Tests of Unclear Etiology

Liver biopsy has long been regarded as an important diagnostic adjunct in the evaluation of abnormal liver tests of unclear etiology—that is, after a thorough history, physical examination, biochemical, serological, and imaging investigation have failed to elucidate a diagnosis. Available data indicate that liver histology will, in a proportion of patients, point to a specific diagnosis[51] and lead to a change in patient management.[52,53] In one study,

Table 4. Use of Liver Biopsy in Clinical Practice

	Diagnosis	Staging	Prognosis	Management
Hepatitis B	–	++++	+(+)	++
Hepatitis C	–	++++	+(+)	++++
Hemochromatosis	+	++++	+(+)	+
Wilson Disease	++	++++	+	–
AI-AT	+	+++	+(+) (depends on whether lung disease	(+)
AIH	+++	++++	+(+)	++++
PBC	++ (AMA-negative; ? overlap syndrome)	++++	+++	++
PSC	++ (small duct disease; overlap syndrome?)	+	–	(+)
Alcohol	+(+)	+++	++	(+)
NAFLD/NASH	+++	+++	+(+)	(+)
HCC	++ (depends on size)	–	–	++++
Other focal lesions	++	–	–	++
Infiltrative	++++	+(+)	(+)	+(+)
DILI	++	+	+	+
Acute liver failure	+(+)	–	–	++ (depends on diagnosis)
Post-OLT	++++	+++	+(+)	+++

Abbreviations: A1-AT, alpha1-anti-trypsin disease; AIH, autoimmune hepatitis; AMA, antimitochondrial antibody; DILI, drug-induced liver injury; HCC, hepatocellular carcinoma; NAFLD/NASH, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

histological findings were examined in 354 patients who underwent liver biopsy to investigate abnormal liver tests; 64% of biopsies revealed an element consistent with NAFLD, while other diagnoses included cryptogenic hepatitis, drug-induced liver injury, primary and secondary biliary cirrhosis, AIH, alcohol-related liver disease, primary sclerosing cholangitis (PSC), hemochromatosis, and amyloid and glycogen storage disease.[53] Only 6% of patients had a normal liver biopsy, whereas 26% were found to have some degree of fibrosis and 6% of patients had cirrhosis. Patient management was modified in 18% of patients after liver biopsy, and three families were entered into a screening program for heritable liver disease.[53] Thus, it was concluded that the finding of abnormal liver tests in the absence of diagnostic serology may indicate significant liver disease and histological analysis provides meaningful information. Conversely, in another study, asymptomatic adult patients with persistent ($\geq$ 6 months) liver test abnormalities were examined (patients with a strong suspicion for a specific liver disease were excluded).[52] In this study of 36 patients, a presumptive diagnosis and a preliminary management plan were documented before liver biopsy; prebiopsy diagnoses included nonalcoholic steatohepatitis (NASH; 24 patients), AIH (3 patients), PBC (2 patients), PSC (2 patients), and others (5 patients). Histological findings after liver biopsy changed the diagnosis in only 14% of cases. Thus, although the liver biopsy appeared to help confirm the diagnosis, biopsy findings infrequently altered the suspected prebiopsy diagnosis, and even more rarely altered management.[52] Liver histology may also be helpful in the establishment of an unsuspected diagnosis, such as alcoholic liver disease.[54,55] Particularly in the setting of abnormal liver tests of unclear etiology, the risks and benefits of a liver biopsy should be carefully weighed, and the decision to perform a liver biopsy must be individualized.

Cryptogenic Cirrhosis

Cryptogenic cirrhosis or cirrhosis of unknown etiology is found to be the assigned diagnosis in 3%-30% of patients with cirrhosis.[56,57] Cryptogenic cirrhosis has several putative causes including NASH, silent or "burnt out" AIH, occult viral infection, and covert alcoholism. Based on well-documented serial biopsy reports demonstrating progression of prior histological NASH to cirrhosis without any continuing definitive evidence of NASH[58-60] and based on extensive epidemiological data, NASH is considered one of the leading causes of cryptogenic cirrhosis in many western countries,[61-63] although autoimmune disease appears to be a more common underlying disease in some parts of Europe.[64,65] Classification schemes for cryptogenic cirrhosis have been proposed on the basis of the clinical setting and on so-called residual histological findings such as foci of autoimmune-like inflammatory infiltrates versus NASH-like foci of steatosis, cellular ballooning, and glycogenated nuclei.[66,67] Indeed, a recent serial biopsy study of patients with cirrhosis who had an-

tecedent biopsies revealing NASH support the use of these parameters as markers for prior NASH.[68]

Liver Transplantation

Assessment of liver histology following orthotopic liver transplantation is an essential component of management in this patient population. It is often important to make a specific diagnosis in the setting of liver test abnormalities early after transplantation to investigate allograft rejection, preservation or reperfusion injury, drug-induced liver injury, (usually recurrent) viral infection, or bile duct injury. Liver biopsy is also often helpful in the setting of late allograft dysfunction,[69] including to investigate the possibility of recurrence of the original disease.[70] Some liver transplant programs perform liver biopsy on a protocol basis after transplantation (e.g., annually), even in those patients with normal liver tests, although compelling evidence to support this approach is lacking. In contrast, there is good evidence suggesting that fibrosis progression may be predicted by using liver histology in patients following transplantation.[35,71] In one study, liver histology obtained at 1 year after transplantation in patients with HCV infection allowed identification of patients with rapid fibrosis progression (donor age $>$ 55 years was associated with rapid fibrosis progression and development of cirrhosis).[71] In another study, patients with more advanced fibrosis stages had a greater likelihood of clinical decompensation than those with minimal or no fibrosis.[35]

In addition, histological assessment appears to be critical in evaluation of the donor liver immediately before it is transplanted. Macrovesicular steatosis, (occult) fibrosis, and inflammation have all been associated with poorer graft function after liver transplantation, especially in older recipients and those with chronic HCV liver disease. Some experts have recommended that donor livers with suspicious clinical histories be evaluated by sampling at least two sites.[72] Importantly, while liver ultrasound has high specificity for exclusion of steatosis in apparently normal livers, both its sensitivity and negative predictive value are very low, thus limiting its utility in the diagnosis of a fatty liver.[73]

Liver biopsy and evaluation of hepatic histology in evaluation of healthy living related donors is controversial.[74-76] In a study of 144 donor candidates who underwent liver biopsy as part of the pretransplant donor evaluation, 31 (21%) had at least one histological finding precluding liver donation (21 had steatosis and 10 had other diseases, including non–A-D hepatitis in six cases, diffuse granulomatosis in two, schistosomiasis in one, and cryptogenic fibrosis in one).[74] Another study found that approximately half of presumably healthy donors had abnormal pathology results, including nearly one-third of patients with fatty changes.[76] Thus, some experts believe that preoperative liver biopsy is a necessary component of the evaluation of potential living donors.[74,76]

Focal Disease and Mass Lesions

The use of liver biopsy for evaluation of focal liver disease (i.e., a lesion detected by imaging) is highly variable and difficult. Evaluation of focal liver disease is further complicated because lesions may be cystic, solid, or vascular (or combinations thereof) and because there is considerable overlap in the appearance between benign and malignant lesions. Further, use of liver biopsy almost always depends on the specific clinical scenario. For example, evaluation of mass lesions requires consideration of whether the patient has no known underlying liver disease or whether the patient has a known parenchymal liver process. Both categories of patient may require consideration of liver biopsy in establishing the correct diagnosis. Initially, cross-sectional imaging may confirm that the liver has an abnormal contour consistent with cirrhosis, and may demonstrate other features of portal venous hypertension such as splenomegaly and intra-abdominal varices. Moreover, the liver may be enlarged because of the presence of the lesion(s).

In patients with underlying liver disease, especially cirrhosis, the overriding concern is with HCC. This diagnosis can be made in patients with a typical lesion (usually $>$ 2 cm in size, with a typical vascular pattern seen with dynamic imaging techniques).[77] In patients with smaller lesions, the use of liver biopsy (typically fine-needle aspiration biopsy) is controversial.[78,79] Arguments against biopsy sampling include: (1) sampling error may leave the diagnosis in doubt; (2) HCC recurrence rates after liver transplantation were significantly higher among patients with tumors larger than 3 cm, pathological tumor-node-metastasis (pTNM) I-III stage, Child class B or C cirrhosis, and alpha-fetoprotein $>$200 ng/mL who underwent biopsy;[80] and (3) there appears to be a small, but finite risk of tumor seeding of the needle track through which the biopsy was procured (see below under contraindications).[81-83] Conversely, the presence of HCC significantly alters the priority for liver transplantation, leading to the need to avoid false positive imaging studies; thus, histological confirmation may facilitate management by removing doubt. Uncertainty regarding these issues underlies the reported wide practice variation.[84,85]

For specific recommendations about liver biopsy in patients with suspected HCC, see the AASLD practice guideline review on this subject.[77] Part of the controversy about liver biopsy in patients with suspected HCC derives from previous limitations in therapeutic options and the

Table 5. Hepatic Mass Lesions

Benign
Cysts
Hemangioma
Adenoma
Liver abscess (amebic or pyogenic)
Focal nodular hyperplasia
Fatty infiltration
Rare primary liver neoplasms
Malignant
Hepatocellular cancer
Cholangiocarcinoma
Metastatic
Rare primary liver neoplasms
Rare primary bile duct neoplasms

lack of predictive utility of simple histological characteristics such as the degree of differentiation.[86] This area is likely to change as new treatment modalities emerge (e.g., radioactive beads and anticancer biological agents) in conjunction with a better understanding of HCC biology, which might predict response.

Another mass lesion that may develop in the setting of underlying liver disease is cholangiocarcinoma. Although isolated lesions may occur in otherwise normal livers, this lesion typically arises in the presence of chronic biliary tract disease, e.g., PSC or a choledochal cyst. It usually presents as a solitary lesion either involving the biliary hilum or within the hepatic parenchyma. The decision to biopsy such a lesion, assuming it is solitary, may be governed by whether surgical resection is considered feasible. If not, or the possibility of liver transplantation arises, then the lesion should be biopsied under image guidance. Any enlarged porta hepatis or other upper abdominal lymph nodes may be biopsied at the same time. It may not be possible to distinguish rare primary hepatic tumors from a more common primary lesion or a solitary metastasis solely on the basis of cross-sectional imaging and tumor markers, in which case image-guided biopsy is also necessary to confirm the diagnosis.

The gastroenterologist and hepatologist, whether working in the community or in an academic setting, may anticipate referral of patients whose principal problem is the recent discovery of one or more focal hepatic lesions in the absence of underlying parenchymal/structural liver disease. This may arise after an imaging test due to specific symptoms or signs, or perhaps after imaging undertaken for reasons that may have nothing to do with the hepatic lesions. Patients who do not have parenchymal liver disease and in whom a focal hepatic lesion(s) is discovered will often have one of the abnormalities highlighted in Table 5. Virtually any of these lesions may be single or multiple, although overall, most are solitary.

Generally, the most common lesions identified in patients without underlying liver disease include benign hepatic lesions, most often solitary, but on occasion multiple. For the most part, these should have sufficient distinguishing characteristics on high-quality cross-sectional imaging modalities such that liver biopsy is unnecessary. For example, a hemangioma has characteristic bright appearances on the T2-weighted magnetic resonance imaging and often displays dynamic enhancement with contrasted computed tomography (CT) imaging. Likewise, focal nodular hyperplasia is typically solitary and has a "central scar" of low attenuation. Alternatively, where hepatic adenomata are multiple and appear hypervascular on the arterial phase of triple contrast CT imaging, concern may arise for metastases from, e.g., thyroid cancer, thus making biopsy of one or more lesions mandatory. Pyogenic liver abscesses may be associated with air produced by gas-forming bacteria.[87]

Apparent metastatic lesion(s) without an obvious primary site may be hypoechoic either hyperattenuating or hypoattenuating (typically they are of low attenuation) on CT imaging, and should be biopsied under image guidance to confirm the diagnosis. If there is any doubt as to whether the patient has underlying parenchymal disease, then biopsy specimens should also be taken from site(s) distant from the lesion(s) also.

The approach to patients with mass lesions will vary depending on the patient's overall clinical picture. Table 6 summarizes some of the more common liver lesions, and their imaging appearances. Because imaging plays a critical role in evaluating essentially all liver mass lesions, it is imperative that they be managed in close association with an experienced imaging expert.

Recommendations

1. Liver biopsy should be considered in patients in whom diagnosis is in question, and when knowledge of a specific diagnosis is likely to alter the management plan (Class I, Level B).

2. Liver histology is an important adjunct in the management of patients with known liver disease, particularly in situations where (prognostic) information about fibrosis stage may guide subsequent treatment; the decision to perform liver biopsy in these situations should be closely tied to consideration of the risks and benefits of the procedure (Class I, Level B).

Technical Issues, Contraindications, and Complications

Preparation for Liver Biopsy. The general approach to liver biopsy has changed substantially over the past 10-20 years. Currently, liver biopsy is typically under-

Table 6. Mass Lesions

Type of Lesion	Radiographic Appearance*	Clinical Features
Simple cyst	Thin walled with homogenous low-density interior on CT imaging	Very common, often incidental
Hemangioma†	Vascular enhancement is often prominent (periphery of the lesion may be prominent) on contrasted CT imaging	The commonest benign hepatic neoplasm
FNH	Contrast-enhanced CT reveals intense arterial phase enhancement and the lesion becomes isoattenuating to liver and difficult to detect in portal venous phase. A central scar typically shows little enhancement in the arterial phase	Commonest in young women
Adenoma	Well-circumscribed, hyperechoic mass on ultrasound. Contrast-enhanced CT shows transient intense enhancement in the arterial phase, followed by rapid washout of contrast in portal venous phase	Commonest in young women (associated with oral contraceptives); may be difficult to distinguish from hepatocellular carcinoma
Focal fat	Nonspherical shape, absence of mass effect, and a low density on contrast enhanced CT	
Hepatocellular carcinoma	On contrast-enhanced CT, tumor enhances in arterial phase and becomes hypoattenuating in portal venous phase	Almost always occurs in the setting of cirrhosis
Cholangiocarcinoma	Solid appearing, with no vascular enhancement	Almost always occurs in the setting of biliary disease
Metastasis	Solid appearing, with variable but typically minimal vascular enhancement	Clinical scenario often consistent with a primary tumor at another site
Liver abscess	Air suggests anaerobic bacteria. Amebic cysts often have a hypodense, water density	Classic clinical scenario includes fever
Hydatic cysts	May have daughter cysts within a thick-walled main cavity	Patients are usually from an area in which the disease is endemic

*Features may be variable for many lesions.
†Some other hypervascular tumors include neuroendocrine/islet cell tumor, carcinoid, renal cell carcinoma, and melanoma.

taken on an outpatient or "same day" basis. Most often, the patient will have been seen in the clinic or office within the preceding month where a discussion about the indications for, benefits, and risks of liver biopsy will have occurred.

Because it is well-appreciated that many patients undergoing liver biopsy experience significant anxiety about the procedure, the following practical points should also be discussed before the procedure: (1) by whom and where the biopsy will be performed, (2) whether sedation of any sort may be taken prior to the procedure, or will be available immediately beforehand, (3) what degree of pain may be anticipated during and after the procedure, and the measures available that might help minimize and/or attenuate it, (4) when the patient may return to their usual level of activity, and to work outside the home if applicable, and (5) when the result will be known, and by what means this information will be communicated to the patient. Being clear and precise about these pragmatic issues are important to facilitate performance of the procedure and instill in the patient a sense of confidence. Written informed consent, including risks, benefits, and alternatives, should be obtained prior to liver biopsy.

Recommendations

3. Prior to performance of liver biopsy, patients should be educated about their liver disease and about investigations other than liver biopsy (if any) that may also provide diagnostic and prognostic information (Class I, Level C).

4. Prior to performance of liver biopsy, patients must be carefully informed about the procedure itself including alternatives (as above), risks, benefits, and limitations; written informed consent should be obtained (Class I, Level C).

Prebiopsy Testing

Common practice includes measurement of the complete blood count, including platelet count, prothrombin time (PT)/international normalized ratio (INR), in some institutions the activated partial thromboplastin time, and/or cutaneous bleeding time at a suitable juncture prior to the biopsy. Some experts recommend having a specimen of blood typed, so that blood could be made available at short notice in case of bleeding. Patients with previously documented abnormalities in laboratory tests may require these to be repeated closer to the time of biopsy; the time frame will vary depending on the specific clinical scenario and local policies. However, as highlighted below, the utility of these tests in predicting bleeding risk is uncertain and generally not supported by the available literature.[88-91] Moreover, the prevalence of more complex hemostatic defects in patients undergoing biopsy, such as hyperfibrinolysis, which are undetectable by conventional tests, is unknown, although some 10%-15% of hospitalized patients with cirrhosis appear to have this particular problem.[92-94] Hyperfibrinolysis should be suspected when there is late (hours) postprocedure bleeding, consistent with initial clot formation and

premature clot dissolution thereafter. Additional studies are needed to assess the preprocedure utility of more global measures of hemostasis such as thromboelastography; this test assesses indices of hyperfibrinolysis and platelet function. Additionally, imaging reports should be reviewed to ensure that (1) no focal lesion exists in the right hepatic lobe, e.g., hemangioma; and (2) that biliary dilation is not present. Either of these conditions might give rise to an otherwise unsuspected (and avoidable) complication.

Prebiopsy and Peribiopsy Preparation and Management

Experts vary in their preference as to whether patients should be fasting prior to biopsy, and data to shed light on the best approach are not available. There is anecdotal evidence that a light snack 2-4 hours before transthoracic liver biopsy may help avoid a vasovagal response during or shortly after the procedure. Some experts ask patients to consume a light fatty breakfast so as to encourage gallbladder contraction (and thus presumably reduce the likelihood of gallbladder perforation). On the other hand, others have raised the possibility that postprandial hyperemia may increase portal blood flow, and could theoretically increase the risk of bleeding. Further, the nonfasting state may create difficulties in the event of a major complication.

Nearly all recommendations regarding periprocedure restrictions lack definitive evidence because few recommendations (other than patient positioning immediately after biopsy; see below) have actually undergone comparative study. However, a number of practices have become established by convention. Usual daily activities may be undertaken up until the day preceding liver biopsy. Following the procedure, patients are encouraged to rest quietly, particularly if they received sedation and/or opiate analgesia afterward. Many physicians recommend that patients who live more than 1 hour traveling distance by car from the center remain close by that evening, in case of potential late complication. However, in the absence of an evident complication or significant pain that necessitates use of potent analgesia, there should be no restriction upon return to work the following day. Patients are discouraged from lifting weights greater than 10-15 pounds, for a minimum of 24 hours, because this may increase intra-abdominal pressure and in theory could facilitate bleeding from the puncture site.

Management of Medications

An important issue surrounds management of antiplatelet (i.e., aspirin, ticlodipine, clopidogrel, IIb/IIIa receptor antagonists, nonsteroidal anti-inflammatory drugs) and/or anticoagulant drugs (i.e., warfarin) before and after the time of liver biopsy. Little data are available with which to guide management about the timing of discontinuation of (or even the need to discontinue) these medications. Indeed, data from other areas in which invasive procedures are performed (i.e., prostate, kidney, breast, gastrointestinal tract) are limited and variable, but the general consensus is that these medications should be discontinued from several to 10 days prior to the procedure.[95-97] It should also be emphasized that the liver is intrinsically different from these other organs (e.g., it is highly vascular), and thus extrapolation of data about biopsy risk at other sites may not be appropriate. Data estimating the risk of bleeding in patients treated with newer antiplatelet agents (adenosine diphosphate receptor antagonists, IIb/IIIa receptor antagonists) are inadequate to make firm recommendations. It is generally recommended that warfarin should be discontinued at least 5 days before the scheduled procedure; the decision to obtain a preprocedure PT should be individualized.[97,98] It is also recognized that antiplatelet and/or anticoagulant drugs are important for certain patients (e.g., an elderly patient with atrial fibrillation in the setting of diminished left ventricular function). Therefore, management of specific drugs should be handled on a case-by-case basis, and in all patients, the risk of discontinuing these medications must be weighed against the (potential) risk of bleeding during/after liver biopsy. In each case, the pros and cons of medication discontinuation versus the need for assessment of liver histology should be weighed carefully. The patient should take other prescribed drugs (e.g., antihypertensive, immunosuppressive therapy, etc.) the morning of the procedure with the aid of a few sips of water.

Data addressing the use of intravenous or subcutaneous heparin or heparin-like compounds in the peribiopsy period are lacking. However, these compounds are generally short-acting and should be able to be stopped in a shorter period of time than warfarin or antiplatelet medications, the latter of which is generally long-acting.

Many patients with diabetes mellitus undergo liver biopsy. For these patients, it is recommended that the patient continue antidiabetic therapy, whether insulin or other agents. Oral agents are generally not an issue but doses of insulin may have to be adjusted in the peribiopsy, particularly if the patient is made NPO (that is, nothing peroral) prior to the biopsy.

Unfortunately, few data are available with which to address the subject of when patients may restart medications that have been stopped prior to liver biopsy, particularly those that may be associated with an increased risk of bleeding. In general, the risk of bleeding after liver

biopsy is greatest within the first several hours after the procedure (see also below) and decreases with time after biopsy. However, reports of delayed bleeding[99,100] suggest that clot dissolution at the biopsy site may occur.

Recommendations

5. Antiplatelet medications should be discontinued several to 10 days before liver biopsy, although there is uncertainty surrounding the need for their discontinuation. Management of specific compounds should be handled on a case-by-case basis, taking into account their clinical indications, as well as the potential bleeding risk associated with their use in the setting of liver biopsy (Class I, Level C).

6. Anticoagulant medications should be discontinued prior to liver biopsy. Warfarin should generally be discontinued at least 5 days prior to liver biopsy. Heparin and related products should be discontinued 12-24 hours prior to biopsy. In all patients, the risk of discontinuing anticoagulant medications must be weighed against the (potential) risk of bleeding during/after liver biopsy (Class I, Level C).

7. Antiplatelet therapy may be restarted 48-72 hours after liver biopsy (Class I, Level C).

8. Warfarin may be restarted the day following liver biopsy (Class I, Level C).

The Liver Biopsy Procedure—Technique and Process

The liver biopsy should be performed in a dedicated area, with adequate space for the operator(s), assistants, emergency equipment if necessary, or for family members during recovery. Use of oral or intravenous anxiolytic therapy or conscious sedation is variable; available data indicate that it is safe when used.[101,102] If such medications are or may be utilized, then any substantial oral intake should be avoided prior to the procedure. Routine placement of an intravenous cannula prior to the procedure is practiced in many facilities as a precaution should there be significant pain and/or bleeding after the procedure, but the cost/risk benefit of this approach is unknown.

Liver Biopsy Methods

1. Percutaneous Biopsy. This method may be undertaken in one of three ways, namely palpation/percussion-guided, image-guided, and real-time image-guided. (Table 2).

A palpation/percussion-guided transthoracic approach, after infiltration of local anesthesia, is the classic percutaneous method (see also below). Although the subcostal approach has been performed in patients with hepatomegaly that extends well below the right costal margin,[103] it is not recommended in routine practice without image guidance.

2. Transvenous (Transjugular or Transfemoral) Biopsy. A number of specific situations warrant consideration of this approach. Patients with clinically demonstrable ascites; a known or suspected hemostatic defect; a small, hard, cirrhotic liver;[104] morbid obesity with a difficult-to-identify flank site; or those in whom free and wedged hepatic vein pressure measurements are additionally being sought (see below) should be considered candidates to undergo liver biopsy by the transvenous route. The technique has been well described in the literature and should be considered standard.[105,106] Expense and availability of local expertise are also important variables when considering transvenous biopsy.

3. Surgical/Laparoscopic Biopsy. In many circumstances, a surgical or laparoscopic approach is utilized because the liver is noted to be abnormal in appearance prior to planned surgery or at the time of surgery. Biopsy in this situation is performed either with typical needle devices or by wedge resection. Notably, the latter has been criticized as producing overestimates of fibrosis due to its proximity to the capsule. Laparoscopic liver biopsy allows adequate tissue sampling under direct vision, with direct (and immediate) control of bleeding. It is generally performed by those with special expertise, typically under general anesthesia. It should be noted that creation of a pneumoperitoneum (with nitrous oxide) is highly reliable and allows the use of conscious sedation and performance of the procedure in specialized areas within an endoscopy unit. Most studies that have compared laparoscopic biopsy to transthoracic percutaneous biopsy have demonstrated greater accuracy in diagnosing cirrhosis with the former approach, probably because of the added benefit of peritoneal inspection.[107-109] Complications of this method include general anesthesia, local abdominal wall or intraperitoneal trauma, and bleeding. Expense and the requirement for special expertise have limited its use.

New laparascopic techniques may facilitate laparoscopic liver biopsy, and could theoretically be performed safely at low cost. An exciting possibility is that techniques extending from natural orifice transluminal endoscopic surgery (NOTES) could be used to perform liver biopsy. In one study, transgastric flexible endoscopic peritoneoscopy allowed systematic visualization of the liver with subsequent liver biopsy (and adequate tissue samples for histologic examination) in a small number of obese patients for whom percutaneous biopsy would have been technically difficult or associated with unacceptably high risk of complication.[110]

4. Plugged Biopsy. The plugged biopsy has been proposed as being potentially safer than standard percutaneous biopsy among certain patients (i.e., those believed to be at high risk for bleeding such as those with coagulopathy and/or thrombocytopenia or a small cirrhotic liver).[111] The plugged biopsy is a modification of the percutaneous method in which the biopsy track is plugged with collagen or thrombin (or other materials) as the cutting needle is removed from a sheath, while the breath is still being held.[112] In one study, the approach was both well-tolerated and safe.[113] In another study, this technique was compared to transjugular liver biopsy among patients with prolonged PT and reduced platelet counts.[114] The plugged-percutaneous liver biopsy technique was quicker and yielded specimens of significantly longer length than the transjugular approach, but was complicated by hemorrhage that required blood transfusion in 2 of 56 (3.5%) of plugged biopsy patients, compared with 0 of 44 (0%) undergoing transvenous biopsy.[114]

Liver Biopsy Devices

Liver biopsy devices originated in the late 1800s, and proliferated in the early 20th Century.[8] The liver biopsy devices used most widely today for diagnosis and management of patients with parenchymal liver disease are the core-aspiration needles (Menghini, Jamshidi, or Klatskin-style) and sheathed cutting needles (either manual or spring-loaded, often referred to as a "Trucut-style" in reference to one of the earliest cutting devices). Newer automated versions of this latter type have recently emerged, allowing variable pitch and specimen length. The cutting needle devices generally pass into the liver parenchyma using a troughed needle before an outer sheath or hood slides over this to secure a core of tissue. This is especially helpful among patients with suspected or established cirrhosis because it limits the tendency for the specimen to shatter or fragment. In general, cutting needles have been shown to produce more reliable specimens in advanced fibrosis, although studies so far have not included the newer variable pitch automated core device (see below).[115]

The caliber of (most) current cutting needles is about 16 gauge (1.6 mm) and the trough length is usually 1.6-1.8 cm, thereby limiting the overall dimensions of the specimen that may be retrieved, and thus the number of portal tracts that may be available for analysis (see below). Conversely, the traditional core-aspiration technique relies on suction generated via a syringe in conjunction with a flat or a beveled (Menghini or Klatskin) needle tip to procure a core of liver tissue. The pressure of suction may cause some specimens, particularly those from cirrhotic livers, to fragment more easily and should be an important consideration in the choice of device. Newer automated core needle devices have recently emerged; these utilize a tiny inflection of the cannula at its tip, which serves to trap the specimen and obviates the need for suction. Thus, longer cores may be obtained without fragmentation.

Liver Biopsy Procedure

Standard transthoracic percutaneous liver biopsy is performed with the patient placed supine in a comfortable position, The right arm and hand should be placed gently behind the head, also in a comfortable, neutral, position. Selective use of sedative medications during liver biopsy may alleviate anxiety[116] and appear to reduce postprocedure pain[117]; their use should be considered to be a matter of local preference and expertise.

The skin is prepped and draped, then anesthetized with a local anesthetic agent, typically lidocaine, 1%. The area from the skin to the peritoneum is also anethestized using care to advance only above the appropriate rib (intercostal arteries generally run below the rib so that intercostal arterial injury can be avoided by inserting the needle over the cephalad rather than the caudad aspect of the rib) and ensuring that anesthesia is not injected into a vascular structure (typically the anesthesia plunger is withdrawn slightly to see that blood does not return, before injection of local anesthetic). Pain with insertion of the biopsy needle indicates inadequate local anesthesia.

The liver capsule itself may be anesthetized using a small, 23-gauge or 25-gauge "finding" needle, but whether this practice is beneficial in the absence of real-time image guidance is unknown (because it is unlikely that the specific portion of the liver anesthetized would subsequently be biopsied). If used, application of the local anesthetic is facilitated by observing the patient's respiratory cycle and instilling the agent during a brief breath-hold. Care should then be taken to perform the biopsy at the same point in the respiratory cycle (usually at a full but not forced expiration) to insure piercing the peritoneum and liver capsule at exactly the same point as application of the local anesthetic agent previously administered.

It is well recognized that the liver physically moves during breathing. Further, because there is concern that the liver may be lacerated if it is moving, breath-holding is often advocated and used during the actual passage of the biopsy needle in the routine transthoracic approach.[118] It is believed to both reduce the risk of capsule laceration and to facilitate biopsy at the site of local (liver) anesthetic if used. Although many techniques have been utilized (i.e., performing biopsy at the end of deep expiration, during simple breath-holding, etc.) and some perform liver biopsy without formal breath-holding,[104] no study has addressed the use of a breath-hold or which technique is best.

Once the liver biopsy has been accomplished, the patient then rests quietly and is carefully observed by experienced nursing staff. Immediately after the biopsy, vital signs are typically obtained at least every 15 minutes for the first hour, and every 30 minutes during the second hour. The patient is often placed in the right lateral decubitus position (presumably to allow the liver to rest against the lateral abdominal wall and thereby limit bleeding), although this is largely performed as a result of longstanding clinical practice. In a study of 90 patients randomized to the right lateral decubitus position, the supine position, or the right lateral decubitus position (30 patients in each group) followed by the supine position, it was found that patients turned to the right lateral decubitus position had greater pain (mean visual analog scale score of 26.5 of 100, compared with 14.2 [$P = 0.026$] and 12.1 [$P = 0.009$] for combined and supine groups, respectively), without a difference in more severe complications.[119] Thus, the need for postbiopsy repositioning on the right side is questionable. It is recommended that patients simply recover in a quiet, comfortable, setting.

The risk of bleeding is greatest initially after liver biopsy; thus, it is recommended that patients be observed carefully over the first several hours after biopsy. Although the optimal length of observation after the liver biopsy has not been firmly established, it appears that an observation period of 2-3 hours is most appropriate. However, in one study involving 3214 subjects undergoing standard outpatient liver biopsies, the recovery time was gradually decreased from 6 hours to 1 hour. The complication rate did not appear to vary with different observation times, with the majority of the complications occurred during the first observation hour.[120] In another study of 500 patients referred by gastroenterologists for US-guided liver biopsy using an 18-gauge needle, patients were placed in the right lateral recumbent position after biopsy and observed for 1 hour in the US department after the biopsy was performed; 496 patients were discharged after 1 hour observation, without complication.[121] Three patients were observed for a further hour due to pain and one patient was admitted because of bleeding. Prolonged observation times appear to be unnecessary after liver biopsy. It should be emphasized that studies of complications after liver biopsy are generally underpowered because of the rarity of the outcome event (i.e., serious complication).

Recommendations

9. Performance of liver biopsy requires an adequate sized and dedicated physical space suitable for focused physician effort as well as safe patient recovery (Class I, Level C).

10. The use of sedation, preferably light sedation, is safe and does not lead to increased procedural risk (Class IIb, Level B).

11. Vital signs must be frequently monitored (at least every 15 minutes for the first hour) after liver biopsy (Class I, Level C).

12. The recommended observation time after biopsy is between 2 to 4 hours and will vary depending on local expertise and practice (Class I, Level B).

Ultrasound Guidance (See Also Below Under Radiological Considerations). Ultrasound guidance helps direct the liver biopsy needle away from the gallbladder, large vascular structures, colon, and lung, and thus has the potential to reduce complication rate. Nonetheless, there is controversy about the use of US. It has been used either in real-time or via a prebiopsy marking technique where the patient subsequently has liver biopsy performed at the marked site. In a study of 631 patients comparing real-time guided US biopsy performed by radiologists to biopsies performed by gastroenterologists/hepatologists after marking, real-time imaging did not appear to offer a significant advantage in terms of complications over immediate prebiopsy marking.[122]

The potential benefit of US was highlighted in a large randomized controlled, but unblinded, trial in which both major complications requiring hospitalization and minor complications such as pain following biopsy were fewer in patients who had US marking of the biopsy site compared to those who had standard, percussion-palpation guided biopsies (the rate of major complications in the two groups was 0.5% versus 2.2%, $P < 0.05$).[123] Conversely, a retrospective study showed that in biopsies performed with US guidance in the radiology department, the risk of major hemorrhage was similar to nationally published figures.[124] In a prospective study of 166 patients with HCV, US-guided biopsies performed in the radiology department were associated with significantly less pain (36.4% versus 47.3%; $P < 0.0001$) than standard percussion-palpation guided Trucut biopsies, although the use of US was found to be slightly more expensive than Trucut biopsy.[125] Cost-effectiveness analyses have suggested that routine US guidance in clinical practice may reduce the cost of liver biopsy (although as would be expected, this depends on the cost of US).[126,127] Finally, it was found that US assessment of the liver immediately preceding biopsy led to a change in the location of the biopsy site in 13% of patients.[128] Nonetheless, use of US, whether marking or in real-time, for routine liver biopsy is variable, and in the United States, US has not gained widespread acceptance.[129,130] The recent intro-

Table 7. Contraindications to Percutaneous Liver Biopsy

Absolute
Uncooperative patient
Severe coagulopathy
Infection of the hepatic bed
Extrahepatic biliary obstruction
Relative
Ascites
Morbid obesity
Possible vascular lesions
Amyloidosis
Hydatid disease

duction of relatively inexpensive, portable US machines with excellent image quality may change this trend.

Recommendations (see also recommendations 24 and 34)

13. Ultrasound guidance with marking of the optimal biopsy site performed immediately preceding biopsy, by the individual performing the biopsy, is preferred, though not mandatory, because it likely reduces the risk of complications from liver biopsy (Class I, Level B).

Contraindications

Specifying contraindications to liver biopsy is fraught with difficulty given the scarcity of data in this area. Additionally, many of the older studies may not be applicable to practice in the modern era. It should also be emphasized that contraindications will vary depending on the physician operator and available local expertise. For this reason, most of the listed contraindications are considered to be relative (Table 7). In daily clinical practice, the considerations that are often of the greatest concern to the care provider include an uncooperative patient, one in whom there is increased potential for bleeding, and the morbidly obese patient. Important specific potential contraindications are highlighted below.

Uncooperative Patients. When performing percutaneous liver biopsy, it is essential that the patient be cooperative (in particular with positioning and breath holding). A theoretical concern is that if the patient inadvertently moves when the biopsy needle is in the liver, then a tear or laceration may occur (which would in turn greatly increase the risk of bleeding). In patients who are felt to require liver biopsy, but who may have difficulty cooperating, the care provider should consider biopsy by the transvenous route, when moderate to deep sedation may be given, or biopsy under general anesthesia. As highlighted above, the use of sedative medications during liver biopsy may help with anxiety[116] and pain[117] and are not believed to either increase or reduce the risk of major complications. However, they must not be used simply to make an uncooperative patient "more" cooperative.

Ascites. Little data are available with which to guide the clinician in the practice of liver biopsy in patients with ascites. From a practical standpoint, it is likely that the liver is likely difficult to "hit" via the standard intercostal approach in patients with moderate or massive ascites. Whether the risk of bleeding in patients with ascites is increased is unclear. One study suggested that CT-guided or US-guided biopsy in patients with ascites was not associated with an increased risk of bleeding.[131] Options for liver biopsy in patients with ascites include total therapeutic paracentesis performed immediately prior to palpation/percussion-guided transcutaneous biopsy or transvenous or laparoscopic biopsy (the latter may also require therapeutic paracentesis, which can be accomplished during the laparoscopy).[131]

Mass Lesions. Although there has been concern about the safety of liver biopsy for some mass lesions, most experts consider biopsy of most liver mass lesions to be a safe and effective means to provide important clinical information. Mass lesions are often biopsied to clarify diagnosis, typically by radiology experts using a real-time imaging technique (see below). Such lesions may be cystic, solid, or vascular. Mass lesions are most often biopsied after visualization of the abnormality during an imaging examination. Most experts prefer that core samples rather than aspirates be obtained if a diagnosis of neoplasia is being entertained. In general, fine-needle aspiration provides cytology, which typically has less diagnostic value than an adequate core biopsy.

Although liver biopsy in patients with mass lesions is generally safe, several important caveats must be considered. First, biopsy of known vascular lesions should generally be avoided,[132] although image-guided biopsy of potential vascular lesions may be safer because a needle path can be selected whereby normal (or nontumorous) parenchyma can be interposed between the liver capsule and the lesion (see also below). Biopsy of potentially malignant lesions should be undertaken with care because it is believed that tumor vessels are more likely to bleed.[132] When US with color Doppler is used to guide the biopsy, larger tumor and liver vessels can also be identified and avoided. Biopsy of malignant lesions is associated with a risk of tumor spread usually along the biopsy track.[81-83] Although potentially a devastating complication, especially in transplant candidates where immunosuppression may predispose to seeded tumor growth, this risk is almost certainly overstated in earlier literature. For example, in a more recent retrospective study of patients undergoing image-guided biopsy of a lesion suspicious for HCC, HCC was diagnosed by biopsy in 74 (63%) of 118 cases,

and an additional 10 were found to have HCC on follow-up; no patient developed evidence of tumor spread along the needle track.[133] Another study estimated the risk of tumor seeding to be 0.13%.[134] Moreover, the risk appears to be decreased with use of a coaxial approach (i.e., utilizing a 17-gauge introducer and an 18-gauge biopsy needle introduced along a coaxial plane).[135] Uncertainties regarding these issues underlie the widespread variation in practice.

Biopsy and/or aspiration of infectious lesions is generally safe. It has been suggested that the presence of an echinococcal cyst (hydatid disease) (Table 7) represents an absolute contraindication to biopsy because it is known that piercing of an echinococcal cyst may be associated with fatal anaphylaxis. However, available data suggest that careful aspiration of these lesions with 19-gauge to 22-gauge needles is relatively safe.[136] Nevertheless, if suspected, some consideration and preparation for possible anaphylaxis is warranted.

Impaired Hemostasis. In the United States, it is standard practice to modify the approach to liver biopsy based on the level of platelets and/or coagulation parameters. Standard percutaneous liver biopsy is often withheld in patients with a PT-INR above 1.5. However, it is critical to emphasize that the relationship of coagulation profiles to the risk of bleeding in patients with chronic as well as acute liver disease is uncertain. In a study of 200 consecutive patients who had liver biopsy performed at laparoscopy using a 1.8-mm-diameter Menghini needle, "liver bleeding time", i.e., the time to spontaneous cessation of surface bleeding as measured by direct laparoscopic observation, did not correlate with abnormalities in the PT, platelet count, or whole-blood clot time.[137] The average liver bleeding time was 4 minutes and 37 seconds $\pm$ 3 minutes and 48 seconds (standard deviation) and in 10 patients with liver bleeding time of longer than 12 minutes, peripherally derived clotting indices were not different from those of other patients.[137] The authors concluded that the PT, platelet count, and whole-blood clotting time are unreliable predictors of the risk of bleeding after liver biopsy and, hence, are of limited value in determining contraindications to this procedure.[137] In addition, it is not truly understood whether impaired platelet function or coagulopathy due to clotting factor abnormalities are important in predicting risk of bleeding after liver biopsy. It has been suggested that platelet function or performance (see below) may be more relevant to bleeding risk than are derivatives of the PT.[138] Finally, the lack of reproducibility of the conventional INR between different laboratories in patients with liver disease is inconsistent with having a set cutoff for this number.[139]

Platelets. Thrombocytopenia, or the presence of dysfunctional platelets, is also commonly considered to be a relative contraindication to biopsy. Platelet level is a particularly important (and common) issue because patients with presumed liver disease may have cirrhosis, portal hypertension, splenomegaly, and platelet sequestration. The presence of advanced liver disease or cirrhosis may also play a role in function. One study demonstrated that patients with a platelet count below 60,000/mL were more likely to bleed than those with higher counts[140]; bleeding occurred in 3 of 13 patients whose platelet counts at the time of biopsy were 60,000/mL or less, compared to no bleeding in 74 patients with higher platelet counts ($P = 0.003$). However, this study was limited by the small sample size, and definitive data proving increased risk at low platelet counts are lacking. Further, an absolute platelet count threshold does not take into account platelet function. Use of bleeding time to ascertain platelet function has varied in clinical practice, and whether it predicts the risk of bleeding remains uncertain.[141,142] Nonetheless, new data has suggested an optimal platelet level in patients with advanced liver disease; in vitro platelet-related thrombin production (an indirect measure of platelet function) was adequate in patients with cirrhosis having platelet levels of at least 56,000,[138] raising the possibility that such a level could serve as a target for the preprocedure platelet count. However, in vivo data proving this concept is not as yet available. Aspirin, nonsteroidal anti-inflammatory drugs, renal dysfunction, or other systemic diseases all appear to influence platelet function, but how they influence the complication rate for liver biopsy remains an open question. Doubts about platelet function, for example in chronic renal failure patients or those who failed to discontinue aspirin within a prescribed timeframe (see above) are probably best resolved by actually measuring platelet function with tests such as the thromboelastogram. In a case-control study of patients with HCV with (case) or without (control) renal failure on dialysis, the risk of bleeding was similar in both groups, without the use of adjuncts such as desmopressin (DDAVP), although the study may have been underpowered.[143]

Conventional Coagulation Parameters. Given that clinically significant hyperfibrinolysis is estimated to occur in 10%-15% of chronic liver disease patients (and it is not detectable by conventional tests)[89,93,94,144] as well as the fact that patients with chronic liver disease typically have abnormalities in measured laboratory coagulation tests, it is not surprising that there is great concern about the risk of postprocedure bleeding in these patients. However, it is relatively well established that the degree of bleeding from the liver puncture site is not necessarily increased in the setting of mildly abnormal blood coagu-

lation parameters in patients with chronic liver disease.[137,145,146] In contrast, a retrospective survey of experience with liver biopsy practices in the United Kingdom including 1500 patients indicated that clinically important bleeding was more common if the INR was greater than 1.5 than if it was between 1.3 and 1.5.[147] However, a recent systematic review of 25 studies addressing bleeding risk in a variety of conditions, including three studies of patients undergoing liver biopsy, failed to demonstrate a clear relationship between bleeding risk and conventional tests of coagulation.[88] An important consideration is that the commonly used PT-INR is derived from coumadin-treated reference ranges and thus lacks applicability to liver disease where there are abnormalities in both the procoagulant and anticoagulant system.[89] As a practical point of reference, a history of spontaneous mucosal bleeding or marked bruising is important because it may indicate the presence of hyperfibrinolysis or a true bleeding diathesis.

It should be emphasized that although alterations in hematological parameters are important when considering the risk associated with liver biopsy, strict cutoffs for PT-INR may not be appropriate in light of the risks associated with plasma infusion. It is often assumed that an abnormal increase in the PT-INR correlates with an increased risk of bleeding and that correcting the abnormal PT-INR with plasma replacement therapy or agents such as recombinant activated factor VII will reduce or eliminate the risk of bleeding. However, the available data do not appear to support these assumptions, particularly in patients with mild coagulopathy defined as an INR of less than 2.0. (see Segal and Dzik,[88] Stanworth et al.,[148] Abdel-Wahab et al.,[149] Triulzi,[150] and Jeffers et al.[151] for review). In aggregate, it is not clear whether prolongation of the INR in chronic liver disease, while of prognostic significance, actually represents a net bleeding diathesis or not. Thus, better tests are needed to more accurately define the net bleeding risk in these patients. A new measure of coagulation in liver disease has recently been introduced, the "INR_{LIVER}"; It recalculates the International Sensitivity Index from a reference point of patients with liver disease rather than coumadin-treated patients as has been the convention.[152-154] Whether this test will provide a reliable measure of bleeding risk remains to be determined, and further studies are clearly needed to assess the full spectrum of potential abnormalities including platelet function and hyperfibrinolysis. Furthermore, this test is not currently available in clinical practice. A history of easy bruising and/or spontaneous bleeding (such as nose bleeds), which has itself been understudied, should nonetheless warrant consideration of further investigation for an occult bleeding diathesis.

Therefore, a large randomized controlled trial of plasma replacement therapy in patients undergoing invasive procedures appears to be warranted, and was initiated. This trial, begun by the National Institutes of Health Transfusion Medicine/Hemostasis Clinical Trials Network[155] and coined the Study of Hemostasis in Invasive Procedures (SHIP) was intended to include 1300 patients with preprocedure INR of 1.3 to 1.9 undergoing invasive hepatic procedures at 16 sites. Adult or pediatric patients were to be randomly assigned to: plasma infusion of 10 mL/kg body weight just before the procedure or no treatment, and bleeding was to be assessed by a postprocedure US and/or changes in hemoglobin level or the need for transfusion.[150] Unfortunately, although this important study was expected to address the question of whether "correction" of coagulopathy with blood products is beneficial prior to performing liver biopsy, slow enrollment led to its closure.

Several conditions are more definitively associated with enhanced risk of bleeding and therefore warrant additional caution. These include patients with factor VIII (FVIII) or IX (FIX) deficiency, von Willebrand's disease and other hereditary bleeding disorders,[156-159] and those with sickle cell anemia.[160] Patients with known underlying coagulopathy requiring liver biopsy represent a challenge, but it should be emphasized that liver biopsy (percutaneous or transvenous) can be performed in these patients (with definitive factor replacement). Nonetheless, the risk-benefit ratio must be carefully considered on a case-by-case basis.

Other. Reports of complications such as "fracture" of the liver or massive hemorrhage in patients with amyloidosis have raised concern about liver biopsy in these patients.[29,30] However, there are not enough good data available to make specific recommendations and thus, patients should be handled on an individual basis.

Recommendations

14. Percutaneous liver biopsy with or without image guidance is appropriate only in cooperative patients, and this technique should not be utilized in uncooperative patients (Class I, Level C).

15. Uncooperative patients who require liver biopsy should undergo the procedure under general anesthesia or via the transvenous route (Class I, Level C).

16. In patients with clinically evident ascites requiring a liver biopsy, a transvenous approach is generally recommended, although percutaneous biopsy (after removal of ascites) or laparoscopic biopsy are acceptable alternatives (Class I, Level C).

Table 8. Factors that May Influence Complication Risk with Liver Biopsy

Patient cooperation
Coagulation status
Operator experience
Use of image guidance
Type of technique (percutaneous/transvenous)
Number of needle passes
Needle diameter
Type of needle

17. Patients who require liver biopsy and who have a large vascular lesion identified on imaging should undergo the procedure using real-time image guidance (Class I, Level C).

18. The decision to perform liver biopsy in the setting of abnormal laboratory parameters of hemostasis should continue to be reached as the result of local practice(s) and consideration of the risks and benefits of liver biopsy because there is no specific PT-INR and/or platelet count cutoff at or above which potentially adverse bleeding can be reliably predicted (Class I, Level C).

Complications

Rational assessment of overall risk in liver biopsy is hampered by the wide variation in the existing literature. Available studies have reported on patients with diffuse parenchymal disease and patients with focal cancer, making it difficult to understand the risk of complications for patients undergoing liver biopsy for the indication of assessment of global hepatic histology. This is especially true of the larger, retrospective survey studies. Many variables may potentially be important in determining the overall risk of a complication (Table 8), although few quantitative data are available and the highlighted factors are largely based on clinical experience and small case series.

Pain. Pain is the most common complication of percutaneous liver biopsy, occurring in up to 84% of patients, including those with relatively mild discomfort.[102] Pain may be more common in those with a history of narcotic dependence but does not appear to be related to approach (i.e., subcostal versus intercostal).[161,162] Interestingly, patients expect the pain associated with standard percutaneous liver biopsy to be greater than it really is (especially women).[163] When present, pain can usually be managed with small amounts of narcotics, typically codeine. Moderate to severe pain is seen in only a small proportion of patients and should raise the possibility of a complication such as bleeding or gall bladder puncture.[164] The mechanism of pain following percutaneous biopsy is most likely a result of bleeding or perhaps bile extravasation from the liver puncture wound, with subsequent capsular swelling, although the exact mechanism for this pain remains uncertain.[101] A decision about when to investigate with imaging and/or to hospitalize the patient for observation due to pain should be made on a case-by-case basis. When pain is severe enough to require hospitalization, radiological evaluation is usually warranted. In this regard, some experts prefer US, whereas others regard abdominal CT (with contrast) to be more definitive.

Bleeding. The most important complication of liver biopsy is bleeding, which when severe occurs intraperitoneally.[165,166] Severe bleeding is defined clinically (heralded by a change in vital signs with radiographic evidence of intraperitoneal bleeding) and requires hospitalization, the likelihood of transfusion, or even radiological intervention or surgery. Such bleeding has been estimated to occur in between 1 in 2500 to 1 in 10,000 biopsies after an intercostal percutaneous approach for diffuse, nonfo-

Table 9. Complications (Bleeding and Death) After Liver Biopsy

Author	Year	N	Bx	Mild (%) (No Blood Tx)	Moderate-Severe (%) (Transfusion or Intervention)	Mortality (%)	Needle Type
Knauer	1978	175	P	0	0.5	0	Cut
Perrault	1978	1000	P	5.9	5.3	0	Mix
Piccinino	1986	68,276	P	N/A	0.2	0.009	Mix
McGill	1990	9212	P	N/A	0.24	0.11	Mix
Janes	1993	405	P	3.2	0.49	0	Cut*
Stone	1996	168	P	2.3	1.7	0.5	Cut
Cadranel	2000	2084	P	3	0.05	0	15G; asp
Firpi	2006	3214	P	18	0.06	0.06	15G; asp
Pawa (non-ESRD)	2007	241	P	0.4	1.2	0.4	14-18G; cut
Pawa (ESRD)	2007	78	P	1.2	0	0	14-18G; cut
Huang	2007	3806	P	N/A	0.32	0	18G
Myers	2008	4275	P	N/A	0.75	0.14	Mix

Abbreviations: N, number; Bx, biopsy; P, percutaneous; Tx, transfusion; asp, aspiration; ESRD, end-stage renal disease; G, gauge. *A total of 92% of the procedures were with cutting needle.

cal, liver disease (Table 9).[103,120,124,132,164-169] The incidence in this setting does not appear to have changed over the past several decades (Table 9).[103,120,124,132,164-169] Less severe bleeding, defined as that sufficient to cause pain or reduced blood pressure or tachycardia, but not requiring transfusion or intervention, occurs in approximately 1 in 500 biopsies.[103,120,124,132,164,165,167-170] Severe bleeding is usually clinically evident within 2-4 hours, but late hemorrhage can occur even up to one week after biopsy.[171] Premature clot dissolution due to liver disease–associated hyperfibrinolysis has been proposed to play a role in some patients, especially in those with delayed bleeding, although this has not been extensively studied.[89]

Based on laparoscopic observations, some degree of bleeding occurs after all percutaneous liver biopsies; intrahepatic and perihepatic bleeding is also detectable by ultrasonography in 18%-20% of patients after percutaneous biopsy.[120,172] Because severe hemorrhage is usually arterial, US guidance would not be expected to identify small arteries and does not appear to significantly reduce the risk thereof (although it reduces the risk of lung or gallbladder puncture).[124] Other factors that are variably reported to be related to the risk of bleeding include operator experience,[169,173-175] needle diameter,[176] and the number of passes taken.[103,132] Whether cutting needles (for example Trucut and automated variants) have a different risk than aspiration needles (i.e., Menghini or Jamshidi) is unknown, although some retrospective data suggests that cutting needles may be associated with slightly greater risk.[165,177]

As emphasized above, accurate prediction of bleeding based on coagulation indices is problematic (see also above); the available data suggest a poor relationship between bleeding and common laboratory tests (such as platelets, PT-INR, etc.).[137,145-147,178] As a result, there is wide variation in "acceptable" prebiopsy coagulation parameters before biopsy.[179] Whether the use of prophylactic blood products alters the risk of bleeding is currently unknown. Further, because of the conventional measures of coagulation correlate poorly with risk of bleeding, recommendations regarding correction of coagulation indices is limited and tempered by the risk of blood product exposure. Methods to limit bleeding, such as tract plugging, are attractive because of a theoretically improved ability to prevent bleeding, but definitive data on this point are lacking.

Transvenous liver biopsy (typically with a jugular approach) is often recommended in patients with a known or suspected bleeding diathesis because it is commonly perceived to be safer. However, critical review of the existing literature suggests that the risk of bleeding (presumably due to capsular hemorrhage) appears to be approximately similar to that associated with standard percutaneous biopsy,[35,105,114,159,180] perhaps related to the risk of capsular piercing with subsequent hemorrhage. In a recent systematic review, minor and major complications were reported in 6.5% and 0.6%, respectively, of 7649 patients after transvenous biopsy.[180] However, it should be emphasized that much of the data comparing transvenous to percutaneous liver biopsy is retrospective and likely subject to substantial selection bias (i.e., it is highly likely that patients suspected to be at risk of bleeding would be referred for transvenous rather than percutaneous biopsy).

Certain types of patients may be at greater risk of bleeding, such as those with chronic renal failure or those with underlying coagulopathy due to congenital abnormalities in coagulation parameters (such as hemophilia), or even those with cirrhosis who may have acquired abnormalities in coagulation parameters (see also above). Use of DDAVP immediately before liver biopsy (0.3 μg/kg body weight) in patients with renal failure undergoing invasive procedures has received considerable attention;[181-183] however, whether the risk of bleeding in patients with chronic renal failure is significantly increased or whether use of DDAVP reduces any risk has not been proven. In patients on chronic renal replacement therapy, dialysis is often performed prior to liver biopsy. The relative safety of percutaneous biopsy without use of DDAVP in patients with end-stage renal disease who were on dialysis was recently reported.[143]

Although little controlled data are available, clinical experience and smaller studies on the use of recombinant activated factor VII in patients with hemophilia suggest that many different surgical procedures can be successfully performed without the life-threatening bleeding complications that would be anticipated without hemostatic treatment. Indeed, it appears that liver biopsy can be safely performed in patients with hemophilia and other congenital bleeding disorders, provided correction of the bleeding diathesis is undertaken prior to the biopsy.[145,157-159,178,184]

Death. Mortality after liver biopsy is usually related to hemorrhage. It is very uncommon after percutaneous biopsy, but precise figures vary widely in the literature (Table 9).[103,120,124,132,164,165,167,169] Death due to bleeding may also be greater after biopsy of malignant lesions than in patients with diffuse parenchymal disease.[168] The most commonly quoted mortality rate is less than or equal to 1 in 10,000 liver biopsies. Mortality after transvenous biopsy was 0.09% (9 in 10,000) in a recent report of 7649 transvenous biopsies but, again, may reflect the selection of higher risk patients for this intervention.[180]

Miscellaneous. A number of other complications

have been reported after liver biopsy.[147] These include pneumothorax, hemothorax, perforation of any of several viscous organs, bile peritonitis, infection (bacteremia, abscess, sepsis), hemobilia, neuralgia, and rare complications such as ventricular arrhythmia with transvenous biopsy.[180] Infectious complications appear to be increased in post-transplant patients who underwent choledochojejunostomy at liver transplantation.[185] Pneumothorax is critical to recognize immediately after biopsy (reduced breath sounds, typical radiographic findings), because it can lead to immediate catastrophic outcomes if not promptly recognized and treated.

Management of Complications. The most critical aspect about management of complications such as bleeding, pneumothorax, and visceral perforation is to recognize that one of these problems has occurred. Suspicion of a potential complication should be high when the patient complains of pain that is out of proportion to the clinical events that surrounded the biopsy, when heart rate and/or blood pressure trends suggest blood loss, or when there is any evidence of extremis. All complications are handled supportively. Bleeding is most often managed expectantly (with placement of large-caliber intravenous catheters, volume resuscitation, and blood transfusion as necessary), although angiographic embolization or surgery is indicated in patients with evidence of ongoing blood loss. As with symptomatic bleeding, pneumothorax may be self-limited but may require more aggressive intervention depending on the severity of symptoms. Visceral perforation is usually also managed expectantly. In most situations, observation is all that is required, although surgical intervention may be needed in the case of gallbladder puncture and persistent bile leak, or in the case of secondary peritonitis.

Recommendations

19. Those performing liver biopsy must be cognizant of multiple potential complications (including death) that may occur after liver biopsy and discuss these appropriately with their patients beforehand (Class I, Level C).

20. Platelet transfusion should be considered when levels are less than 50,000-60,000/mL (this applies whether one is attempting biopsy transcutaneously or transvenously) (Class I, Level C).

21. The use of prophylactic or rescue strategies such as plasma, fibrinolysis inhibitors, or recombinant factors should be considered in specific situations, although their effectiveness remains to be established (Class IIa, Level C).

22. In patients with renal failure or on hemodialysis, desmopressin (DDAVP) may be considered, although its use appears to be unnecessary in patients on stable dialysis regimens (Class IIa, Level B).

23. Patients on chronic hemodialysis should be well dialyzed prior to liver biopsy, and heparin should be avoided if at all possible (Class I, Level C).

Radiological Considerations

Image-guidance for liver biopsy is considered the standard approach in patients with specific lesions identified by imaging (see above) and its use for marking the liver is emerging as an important part of the more common percussion-palpation procedure in patients with diffuse parenchymal disease (i.e., hepatitis C or NASH). Its use for the specific purpose of marking the liver biopsy site has been limited by the following issues: (1) precedent, which favors palpation-percussion guidance; (2) expense, which may be substantial; and (3) insufficient training for the provider who is performing the biopsy, which further has not been well standardized. It may be used in real-time or as an adjunct to verify the position of the liver in the setting of palpation-percussion guidance.

Image-guidance for liver biopsy (either marking or in real-time) should be considered in patients with known lesions and in those with previous intra-abdominal surgery who may have adhesions, allowing avoidance of vascular or other structures in the latter situation. It may be especially useful in specific situations, including: (1) patients with small livers that are difficult to percuss; (2) patients who are obese, making it difficult to identify the liver by physical examination; or (3) patients with clinically demonstrable ascites. Either CT or ultrasonography may be used for guidance, although US is preferred because it allows real-time needle visualization, avoids exposure to ionizing radiation, and is both quicker and less expensive.[186] The use of CT for image guidance is usually reserved for patients with a thick layer of subcutaneous fat through which US may have difficulty penetrating, typically patients who are morbidly obese or when there is marked ascites; this may vary depending on local expertise. Real-time guidance is not only helpful for inserting the biopsy needle through the liver capsule into a nonvascular portion of liver parenchyma but also useful for precise infiltration of the liver capsule with an anesthetic agent. For biopsy performed under real-time imaging guidance, direct infiltration of the anesthetic to an area just beneath the liver capsule may be facilitated by making a small, visible "bleb". One useful technique is to include a few tiny gas bubbles in the needle during capsular anesthesia, thereby leaving an echogenic footprint or target for subsequent biopsy needle placement.

Technical aspects of performing image-guided biopsies are critical to their success and include the following: (1)

choice of a biopsy site where there is adequate parenchyma without major visible vascular structures, fissures, or the gallbladder; (2) use of a biopsy site where the hepatic parenchyma is easily visualized without requiring extreme inspiratory or expiratory breathing maneuvers; and (3) performing the biopsy at a point where the hepatic capsule has been perforated, using tactile or imaging evidence or both, prior to triggering the spring-loaded cutting needle. It is important to emphasize that small arteries which are the likely source of significant postbiopsy hemorrhage rarely can be accurately visualized by US (and thus avoided). Therefore, caution and careful postprocedure monitoring remain essential after image-guided biopsy, as with other liver biopsy techniques.

Although right lobe biopsy is the usual biopsy site in patients with diffuse disease, the choice of where to biopsy the liver using imaging guidance varies according to the operator. On one hand, some (typically radiologists) prefer the left hepatic lobe because it is readily accessible using an anterior epigastric subcostal approach.[187] If the left lobe is small and subcostal, the patient may be required to suspend respiration during deep inspiration in order to position the liver in a more caudal location. This may be difficult in situations in which moderate (conscious) sedation is used. Moreover, the subcostal approach may require steep needle angulation. On the other hand, most operators prefer the right hepatic lobe because it is large and readily accessible using either a subcostal or an intercostal approach. The subcostal approach avoids the lung but may require steep needle angulation and/or deep inspiration in patients with relatively small livers; this technique may be difficult during conscious sedation. Although a gentle breath hold facilitates anesthetic application and avoids capsule laceration, the intercostal approach does not usually require an extreme breath hold. This approach is associated with a small risk of intercostal artery puncture, which can be minimized by inserting the needle over the cephalad rather than the caudad aspect of the rib. Although the intercostal approach is typically closer to the costophrenic sulci, the lung can be easily avoided because it is readily visible as an echogenic structure on US.

The vast majority of liver biopsies performed in the United States have not used image guidance, and there remain questions concerning cost and adequacy of training. Nonetheless, use of real-time US guidance as part of the liver biopsy has distinct advantages. One is the ability to target a region of liver parenchyma that is not susceptible to respiratory variations. That is, as long as the patient is advised against holding respiration in either deep inspiration or deep expiration, needle placement within the liver should be stationary. A further potential advantage of image guidance is the ability to insure that the needle tip has perforated the hepatic capsule prior to triggering the spring-loaded cutting needle. This can be determined not only by watching the needle under real-time US guidance but also by feeling a subtle "popping" sensation as the needle transgresses the fibrous capsule. Failure to penetrate the capsule may result in an inadequate specimen, even though the device has functioned appropriately. A further potential advantage of image guidance is that it may facilitate development of familiarity of not only important anatomy, but of the procedure in general among trainees. It may also provide a greater level of comfort among patients and support staff alike. Alternatively, it could be associated with a false sense of security. Finally, the image-guided approach could improve the quality of specimens obtained and may reduce the complication rate (see above for discussion of US marking and liver biopsy).

Recommendations

24. Image-guided liver biopsy is recommended in certain clinical situations including in patients with known intrahepatic lesions (real-time imaging is strongly preferred) and in those with previous intra-abdominal surgery who may have adhesions. Image-guided liver biopsy should also be considered in the following situations: patients with small livers that are difficult to percuss, obese patients, and patients with clinically evident ascites (Class I, Level C).

Pathological Considerations

Specimen Size and Quality. In order to justify the inherent risk in the procedure, it is essential that the resulting liver biopsy specimen be adequate so as to allow detailed interpretation. This almost always means that the biopsy should be of large enough size to view a representative amount of parenchyma and number of portal tracts (an adequate number of portal tracts has been proposed to be greater than 11[188,189]); the number of portal tracts is proportional to biopsy size.[190] It should also be recognized that literature assessing biopsy length has focused on size after formalin fixation, and that formalin fixation results in biopsy shrinkage. In one study that examined 61 Trucut biopsy (obtained with a 16-gauge needle) specimens from patients with various types of liver disease, there was shrinkage of biopsies from 19.6 $\pm$ 3.5 mm (measured immediately before formalin fixation) compared to 18.3 $\pm$ 2.9 mm (measured after fixation, before paraffin embedding).[191] Although in occasional instances even a very small biopsy specimen may be large enough to establish a diagnosis (so long as key lesions of the disease process are present), it must be emphasized that in nearly

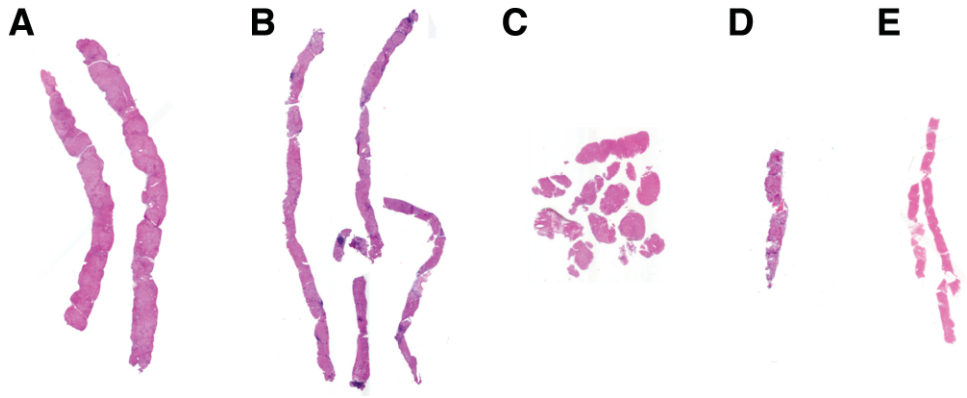

Fig. 1. Specimens of liver biopsies obtained with various sized needles and differing techniques. All five biopsies shown in this figure were submitted for grading and staging of chronic hepatitis C. However, only (A) and (B) are felt to provide enough tissue for adequate histologic analysis. (A) Shown is a biopsy specimen 2.7 cm in length obtained with two passes of a 16-gauge cutting needle. (B) Shown is a biopsy specimen 4.8 cm in length obtained with three passes of an 18-gauge cutting needle. (C) Shown is a fragmented biopsy, 1.1 cm in total specimen length, obtained with a 16-gauge suction needle. (D) Shown is a biopsy specimen 0.5 cm in length obtained with an 18-gauge needle. (E) Shown is a biopsy specimen 1.5 cm in length obtained with a 20-gauge needle.

all liver diseases, parenchymal abnormalities are irregularly distributed, and sampling variability is almost inevitable. For example, with a single pass, even when more than 1.5 cm of tissue was obtained (see below for discussion of biopsy size) steatohepatitis could not be distinguished from simple steatosis in 14% of cases.[192]

Sampling error is minimized by obtaining biopsies from different lobes; although this approach is rarely undertaken in daily clinical practice provided an adequate specimen is obtained from a single site, it may be helpful in certain diagnostic dilemmas. Thus, the most practical way to minimize sampling error is to obtain a biopsy specimen of sufficient size. In turn, it is essential to recognize that the size of the sample is proportional to the size of needle used for sampling; therefore, 16 gauge (or wider) needles appear to be essential to obtain an appropriate specimen, except when sampling focal neoplastic lesions, in which case more narrow gauge cores may suffice. For example, in one study, both grade and stage of viral hepatitis were significantly underestimated with 1-mm-diameter (18 gauge) samples, regardless of their length.[188]

Optimal biopsy length is the subject of intense debate, because an accurate diagnosis of some diseases can be made with short samples. This issue is also confounded by the observation that there may be shrinkage after formalin fixation, and that biopsy length reported by the hepatologist at the bedside is often reported on the unfixed specimen, whereas the pathologist reports the size of the fixed specimen. Studies in patients with viral hepatitis have shown that grading and staging accuracy is reduced in biopsies less than 2.0 or 2.5 cm in length.[188,193,194] In a group of 161 liver biopsies from patients with chronic hepatitis B and C virus liver disease, reduced biopsy length led to an increase in the number of cases with grade levels as follows: 49.7% in those with a 3 cm or greater core, 60.2% in those with $\leq$ 1.5 cm core, and 86.6% in $\leq$ 1 cm long specimens (differences, $P < 0.001$).[188] Similarly, cases staged as having mild fibrosis significantly increased in shorter specimens: 59% in those with a 3 cm or greater core, 68.3% $\leq$ 1.5 cm core, and 80.1% in $\leq$ 1 cm long specimens (differences, $P < 0.001$).

Although a 1.5 cm biopsy specimen may be adequate for assessing many liver diseases,[169] short specimens may result in difficulties in patients with cirrhosis. Such short specimens may lead to a failure to recognize cirrhosis in up to 20% of cases.[195,196] To assess for the presence of cirrhosis, cutting needles are superior to suction-type needles.[115,197]

Thus, long and wide (an ideal size is 3 cm long after formalin fixation obtained with a 16 gauge needle) biopsies are desirable (this may also help justify the risk-benefit of the procedure despite the possibility that the risk associated with use of a larger needle may be theoretically greater) and if cirrhosis is suspected, a cutting needle rather than a suction needle should be used (Fig. 1). Whereas biopsies performed with narrower gauge needles (i.e., smaller than 18 gauge) are often adequate to establish a diagnosis of malignancy, it should be kept in mind that for diagnosis, grading, and staging of non-neoplastic, diffuse parenchymal liver disease, use of a thin biopsy needle may lead to error in up to two-thirds of patients.[198] With transvenous biopsy, it has been suggested that 3 cores be obtained with the typical 19-gauge needles to minimize sampling error.[199]

Tissue Allocation. Depending on the clinical situation, liver tissue obtained by biopsy may be required for several purposes. As a result, allocation of tissue at the

bedside must be optimized. Most of the specimen should be fixed in 10% neutral buffered formalin or other fixative preferred by the local laboratory, because this will usually allow the full range of stains, both routine histochemical (hematoxylin & eosin and Masson trichrome) and immunohistochemical. If less than 2 cm of tissue is obtained, then it should be recognized that taking part of the specimen for uses other than routine histology might compromise standard light microscopic interpretation of the specimen in some situations (i.e., leading to misdiagnosis or mis-grading or mis-staging).

If Wilson disease is strongly suspected, then a quantitative analysis of tissue copper content may be of great value, so part of the specimen may be needed for quantitative copper analysis, even if the biopsy is not large. However, it should be noted that evaluation of copper content is possible in formalin-fixed tissues (including from paraffin-embedded tissue blocks). If iron overload is suspected, staining for iron on routinely processed tissue has similar diagnostic efficacy as the more highly regarded quantitative assays.[200,201] As with quantitative copper assessment, tissue from the paraffin-embedded tissue block may also be used to measure iron.[202]

Electron microscopy is of limited use in diagnosis, with the exception being in research and in some metabolic diseases; if required, a small (1-2 mm) piece of the biopsy may be fixed in glutaraldehyde and processed for electron microscopy. Similarly, a small piece of the biopsy may also be frozen in embedding medium for frozen sections to demonstrate tissue components, such as lipids and porphyrins that will not survive processing in aqueous and organic solvents, or for immunostaining to demonstrate labile antigens that may be destroyed by tissue fixation. A portion of the tissue may be used for culture if bacterial, mycobacterial, or fungal infection is suspected. Tissue may also be flash (or "snap") frozen for other molecular studies or research investigations, provided that the amount left for standard microscopic analysis is of sufficient size so as to allow adequate interpretation. Therefore, procurement of an appropriate specimen is critical both for routine diagnosis and for a number of potentially important ancillary studies.

Tissue Processing. Processing of the tissue and preparation of microscopic sections involve a number of technical issues that are beyond the scope of this guideline. Microscopic sections obtained must be stained for evaluation with hematoxylin & eosin or a similar stain, such as hematoxylin-phloxine-safranin, and then supplemented with other stains tailored to the individual case requirements. A stain for connective tissue is essential to assess hepatic fibrosis. Masson trichrome is used most often in the United States, but many others are available (i.e., such as reticulin or sirius red, the latter of which has recently been used in computer-assisted morphometric quantification of fibrosis).

Other usefule techniques include stains for copper in chronic cholestatic disorders as well as in Wilson disease, stains for iron in iron overload and the periodic acid–Schiff stain after diastase digestion to identify the globules characteristic of alpha-1-antitrypsin deficiency. Numerous antibodies are available for the immunohistochemical identification of specific antigens in tissue, but while useful for research, few of these have validated diagnostic applications. HBV staining for core and/or surface antigen may have clinical application in certain situations; immunohistochemical stains for ubiquitin can identify Mallory bodies more accurately in steatohepatitis and stains for alpha-1-antitrypsin can confirm the diagnosis of alpha-1-antitypsin deficiency. Some stains, such as alpha-fetoprotein and hepatocytes paraffin-1 (HepPar-1) are also useful for classification of tumors such as HCC, although the clinical significance, i.e., correlation of specific staining pattern(s) with therapeutic response and outcome has not been adequately investigated.

Specimen Interpretation. Of similar importance to adequate specimen size is the necessity that a pathologist experienced in liver disease interpret the biopsy, ideally in partnership with the clinician who performed the biopsy and/or whom is caring for the patient. In the absence of this interaction, diagnostic errors (including clinically meaningful ones) by nonspecialist pathologists have been reported in more than 25% of patients evaluated at an academic center.[203,204] Liberal use of second opinions from specialist liver pathologists is also recommended.[203-205]

Assessment of disease severity with liver histology is supported by an extensive body of literature.[206] Complex scoring systems, such as the Knodell scoring system[207] and its revised form, the Ishak scoring system,[208] have been devised for grading and staging of chronic viral hepatitis, and there is now a similar score for steatohepatitis.[209] However, these are not highly reproducible and are only appropriate for statistical analysis of (large) cohorts of patients in clinical trials. For individual patients, it is best to use simple grading and staging systems with three to four categories such as that of International Association for Study of the Liver (IASL),[210] Batts-Ludwig,[211] or Metavir[212] (Table 10). The IASL system, which uses verbal diagnoses rather than numbers, leaves much less room for ambiguity and is therefore preferable. Although simplified systems appear to be the best overall, certain clinical situations, in which the staging of incomplete cirrhosis or Ishak stage 5 may be frequent or perisinusoidal fibrosis, such as with NASH, may lend themselves to

Table 10. Comparability of Terms in Three Simple Systems for Histologic Grading and Staging of Chronic Hepatitis: IASL, Metavir, and Batts-Ludwig*

IASL	Metavir	Batts-Ludwig
Grade (Activity, Inflammation)		
Minimal chronic hepatitis	A1	Grade 1
Mild chronic hepatitis	A1	Grade 2
Moderate chronic hepatitis	A2	Grade 3
Severe chronic	A3	Grade 4
Stage (Fibrosis)		
Mild—Portal fibrosis	F1	Stage 1
Moderate—Periportal fibrosis or portal-portal septa	F1	Stage 2
Severe—Bridging fibrosis (few)	F2	Stage 3
Severe—Bridging fibrosis (many)	F3	Stage 3
Cirrhosis	F4	Stage 4

*See references cited in text.

the more complex systems. This is an area in which better data would allow more precise algorithms.

Recommendations

25. Because diagnosis, grading, and staging of non-neoplastic, diffuse parenchymal liver disease is dependent on an adequate sized biopsy, a biopsy of at least 2-3 cm in length and 16-gauge in caliber is recommended (Class I, Level C).

26. It is recommended that if applicable, the presence of fewer than 11 complete portal tracts be noted in the pathology report, with recognition that diagnosis, grading, and staging may be incorrect due to an insufficient sample size (Class I, Level C).

27. If cirrhosis is suspected, a cutting rather than a suction needle is recommended (Class I, Level B).

28. In clinical practice, use of a simple (e.g., Metavir or Batts-Ludwig) rather than complex (e.g., Ishak) scoring system is recommended (Class I, Level C).

Pitfalls of Liver Biopsy—Sampling Error

Although liver biopsy clearly provides important diagnostic and prognostic information and helps define treatment plans, it must be recognized that liver biopsy may be associated with sampling variability. For example, in a study of 124 patients with chronic HCV infection who underwent laparoscopy-guided left and right lobe liver biopsies,[196] 33% of cases had discordant results by at least one histologic stage (modified Scheuer system). A smaller, but substantial proportion of biopsies were discordant by at least two stages. Similarly, a single liver biopsy specimen may fail to distinguish steatohepatitis from simple steatosis and may mis-stage the disease by one or less frequently two stages if the specimen is much smaller than 2 cm.[192] Thus, although even small biopsy specimens may be sufficient for diagnostic purposes in certain situations, the possibility that sampling variability exists must be recognized, so that the absence of key findings does not necessarily rule out a suspected diagnosis. Indeed, sampling variability appears to be one of the major limitations of liver biopsy.

Noninvasive Alternatives to Liver Biopsy

Given the invasive nature of liver biopsy, a great deal of effort has been directed toward developing noninvasive methods of evaluating liver disease (a review of the multiple noninvasive approaches is beyond the scope of this guideline; for review, please see Rockey and Bissell[5]). In brief, many different serum tests have been studied, and several are commercially available; however, at this time, they are primarily useful for detecting advanced fibrosis or for excluding minimal or no fibrosis.[5] They are not quantitative and are insufficiently precise for assessing disease progression or the effect of therapy. Novel imaging techniques, such as measuring the elasticity of the liver using transient elastography, may assess fibrosis more directly.[213] However, the use of such techniques in routine clinical practice has not been well defined.[6] A wide variety of other imaging techniques may become available, including magnetic resonance spectroscopy, but require further investigation. Given the invasive nature of liver biopsy, and the need for simple and noninvasive methods to assess hepatic fibrosis and/or architecture, it is likely that such tests will continue to emerge and will likely be utilized more widely in clinical practice.

Recommendations

29. Liver biopsy is currently a fundamentally important tool in the management of patients with liver disease, important for diagnosis as well as staging of liver disease and its use is recommended until clearly superior methodologies are developed and validated (Class IIB, Level C).

Training for Liver Biopsy

In the absence of specific data assessing training requirements, it is the opinion of these authors that specific training in percutaneous liver biopsy is required before its performance by new operators. Current specific requirements for training in liver biopsy are based entirely on empirical evidence and experience accrued over the roughly six decades since introduction of the procedure into common practice. Indeed, the number of biopsies required to become adequately trained is unknown. Perhaps the most critical element of liver biopsy training is the need for a skilled preceptor. The AASLD's Training

and Workforce Committee has recommended that the minimum number of procedures required to achieve training proficiency in standard transthoracic percutaneous liver biopsy is 40 (supervised) biopsies; this number is consistent with the requirement for accreditation for advanced training in Hepatology (see the Gastrointestinal Core Curriculum on the American Gastroenterological Association website). The number to become an expert will vary depending on the skill of the operator, the educator, and specifics of the training setting. The educator is expected to have performed more than several hundred liver biopsies so as to have observed or experienced most potential complications. Although percussion-palpation guidance is a standard established by many years of precedent, available data indicates that US guidance may reduce the risk of complications.[127,214] Therefore, training in US should also be developed as part of the required training for percutaneous liver biopsy.

Use of image guidance, whether to mark the liver for subsequent biopsy or in real-time, requires specific experience, which to a large extent has already emerged in gastrointestinal-hepatology units (via the widespread use of endoscopic US and the increasingly common use of small portable US devices in liver/endoscopy units). The level of training required by radiologists to become expert at liver biopsy is also unknown. Appropriate training in image-guidance to identify the liver and mark the skin for subsequent biopsy involves the following aspects: (1) a general knowledge about US device itself and, because the ability to obtain an adequate image is critical, (2) familiarity with the sonographic appearance of the liver, intrahepatic vessels and bile ducts, and perihepatic structures, such as the lung, heart, gallbladder, right kidney, and bowel. Use of prebiopsy image guidance and marking compared to real-time imaging does not appear to influence outcomes.[122] In most instances, use of US to confirm a site is the most practical application of image-guidance technology; greater experience by a broader group of practioners, including hepatologists, is needed in this area.

Recommendations

30. Specific training for liver biopsy is essential and is recommended for those who perform it (Class I, Level C).

31. Liver biopsy should be taught to trainees by experts, highly experienced in the practice of liver biopsy and management of its potential complications (Class I, Level C).

32. Although the number of biopsies required to become adequately trained is unknown, it is recommended that operators perform at least 40 biopsies (Class I, Level C).

33. Training in percutaneous liver biopsy should include specific training in ultrasound interpretation of fundamental liver anatomy and other landmarks (Class I, Level C).

34. Image-guided liver biopsy should be taught to trainees by experts who themselves have adequate training and experience with the technique (Class I, Level C).

Suggestions for Future Research

The use of liver biopsy to obtain tissue for histological interpretation is a long-standing pillar of the practice and science of hepatology and remains a standard for diagnosis and treatment to which numerous other tests are held. Much has been learned about the pitfalls of sampling error and the need to obtain adequate samples so as to minimize this error and about which approaches and devices are most likely to produce good results in different patients. The recent introduction of even more reliable needle devices will undoubtedly further enhance this area. In terms of safety and comfort, it appears that some sort of image assistance (usually US) improves certain outcomes, particularly in the hands of less experienced operators. This technology, long available in radiology units and increasingly available in liver/endoscopy units, may also reduce the time needed to become proficient in biopsy but likely does not reduce the rate of postprocedure bleeding which, although infrequent, requires careful vigilance.

Nonetheless, many questions about liver biopsy remain and the entire area requires much more research. For example, it is not clear which biopsy devices or techniques are best, or the degree to which coagulation abnormalities influence the risk of bleeding complications. With regard to this latter point, assessment of bleeding risk by conventional coagulation indices remains murky at best and is in need of the following research: (1) Which tests are most applicable to predict the risk of bleeding? (2) How will specific results translate into preventive strategies? (3) Will implementation of such strategies affect outcomes? Clearly, we need to understand whether correction of an abnormal coagulation test or platelet level leads to a reduced risk of bleeding (and in particular, relative to the risk and costs of agent administration). Use of plasma or other procoagulants in a preventive strategy to correct a prolonged PT-INR is the most problematic of these issues. In addition, future study is required to develop effective noninvasive alternatives to liver biopsy. Finally, data in the area of training are required, not only to understand how many biopsies are required for proficiency, but also to determine ways to effectively disseminate knowledge of the procedure from current experts to trainees.

Specific suggested areas for future research are as follows:

- Evaluation of platelet and coagulation abnormalities and risk of liver biopsy complications.
- Study of the risk of bleeding after liver biopsy in patients taking or having stopped antiplatelet and/or anticoagulant medications.
- Study to better characterize the potential benefits of real-time image-guided liver biopsy in clinical practice.
- Examination of the utility of specific histology scoring systems in specific diseases in clinical practice.
- Investigation of training requirements.
- The development of effective, noninvasive alternatives to liver biopsy.

Acknowledgment: This guideline was produced in collaboration with the Practice Guidelines Committee of the AASLD. This committee supplied extensive peer-review of the manuscript. Members of the AASLD Practice Guidelines Committee include Margaret C. Shuhart, M.D., M.S., (Committee Chair); Gary L. Davis, M.D. (Board Liaison); Kiran Bambha, M.D.; Andres Cardenas, M.D., MMSc.; Timothy J. Davern, M.D.; José Franco, M.D.; Steven-Huy B. Han, M.D.; Stephen A. Harrison, M.D.; Charles D. Howell, M.D.; Simon C. Ling, MB-ChB, MRCP; Lawrence U. Liu, M.D.; Paul Martin, M.D.; Robert S. O'Shea, M.D.; Nancy Reau, M.D.; Bruce A. Runyon, M.D.; Jayant A. Talwalkar, M.D., MPH; John B. Wong, M.D.; and Colina Yim, R.N., M.N.

References

1. Eddy DM. A Manual for Assessing Health Practices and Designing Practice Guidelines. Philadelphia, PA: American College of Physicians; 1996: 1-126.
2. Position and policy statement: American Gastroenterological Association policy statement on the use of medical practice guidelines by managed care organizations and insurance carriers. Gastroenterology 1995;108: 925-926.
3. American Heart Association Methodology Manual. http://www-.heart.org/presenter.jhtml?identifier=3039683. Published April 2006. Accessed November 2008.
4. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003;139:493-498.
5. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. HEPATOLOGY 2006;43:S113-S120.
6. Rockey DC. Non-invasive assessment of liver fibrosis and portal hypertension with transient elastography. Gastroenterology 2008;134:8-14.
7. Sherlock S. Aspiration liver biopsy, technique and diagnostic application. Lancet 1945;ii:397.
8. Reuben A. Just a second. HEPATOLOGY 2003;38:1316-1320.
9. Czaja AJ, Carpenter HA. Optimizing diagnosis from the medical liver biopsy. Clin Gastroenterol Hepatol 2007;5:898-907.
10. Powell EE, Jonsson JR, Clouston AD. Steatosis: co-factor in other liver diseases. HEPATOLOGY 2005;42:5-13.
11. Powell EE, Ali A, Clouston AD, Dixon JL, Lincoln DJ, Purdie DM, et al. Steatosis is a cofactor in liver injury in hemochromatosis. Gastroenterology 2005;129:1937-1943.
12. Zein CO, Angulo P, Lindor KD. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis? Clin Gastroenterol Hepatol 2003; 1:89-95.
13. Dahlin DC, Stauffer MH, Mann FD. Laboratory and biopsy diagnosis of amyloidosis. Med Clin North Am 1950;34:1171-1176.
14. Manowski Z, Silver MM, Roberts EA, Superina RA, Phillips MJ. Liver cell dysplasia and early liver transplantation in hereditary tyrosinemia. Mod Pathol 1990;3:694-701.
15. Garcia-Tsao G, Korzenik JR, Young L, Henderson KJ, Jain D, Byrd B, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 2000;343:931-936.
16. Roberts EA, Schilsky ML. A practice guideline on Wilson disease. HEPATOLOGY 2003;37:1475-1492.
17. Obici L, Palladini G, Giorgetti S, Bellotti V, Gregorini G, Arbustini E, et al. Liver biopsy discloses a new apolipoprotein A-I hereditary amyloidosis in several unrelated Italian families. Gastroenterology 2004;126:1416-1422.
18. Smanik EJ, Tavill AS, Jacobs GH, Schafer IA, Farquhar L, Weber FL Jr, et al. Orthotopic liver transplantation in two adults with Niemann-Pick and Gaucher's diseases: implications for the treatment of inherited metabolic disease. HEPATOLOGY 1993;17:42-49.
19. Kelly DA, Portmann B, Mowat AP, Sherlock S, Lake BD. Niemann-Pick disease type C: diagnosis and outcome in children, with particular reference to liver disease. J Pediatr 1993;123:242-247.
20. Jevon GP, Dimmick JE. Histopathologic approach to metabolic liver disease: Part 1. Pediatr Dev Pathol 1998;1:179-199.
21. Haagsma EB, Smit GP, Niezen-Koning KE, Gouw AS, Meerman L, Slooff MJ. Type IIIb glycogen storage disease associated with end-stage cirrhosis and hepatocellular carcinoma. The Liver Transplant Group. HEPATOLOGY 1997;25:537-540.
22. Badizadegan K, Perez-Atayde AR. Focal glycogenosis of the liver in disorders of ureagenesis: its occurrence and diagnostic significance. HEPATOLOGY 1997;26:365-373.
23. Panetta J, Gibson K, Kirby DM, Thorburn DR, Boneh A. The importance of liver biopsy in the investigation of possible mitochondrial respiratory chain disease. Neuropediatrics 2005;36:256-259.
24. Heyn RM, Hamoudi A, Newton WA Jr. Pretreatment liver biopsy in 20 children with histiocytosis X: a clinicopathologic correlation. Med Pediatr Oncol 1990;18:110-118.
25. Cole BR. Does liver biopsy provide sufficient diagnostic information to differentiate autosomal recessive from autosomal dominant polycystic kidney disease? Pediatr Nephrol 1994;8:411.
26. Chahal P, Levy C, Litzow MR, Lindor KD. Utility of liver biopsy in bone marrow transplant patients. J Gastroenterol Hepatol 2008;23:222-225.
27. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. HEPATOLOGY 2005;41:1179-1197.
28. Miraglia R, Luca A, Gruttadauria S, Minervini MI, Vizzini G, Arcadipane A, et al. Contribution of transjugular liver biopsy in patients with the clinical presentation of acute liver failure. Cardiovasc Intervent Radiol 2006;29:1008-1010.
29. Volwiler W, Jones CM. The diagnostic and therapeutic value of liver biopsies, with particular reference to trocar biopsy. N Engl J Med 1947; 237:651-656.
30. Reuben A. The legend of the lardaceous liver. HEPATOLOGY 2004;40: 763-766.
31. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. HEPATOLOGY 1999;29:1215-1219.
32. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. HEPATOLOGY 2001;33:1358-1364.

33. Westin J, Nordlinder H, Lagging M, Norkrans G, Wejstal R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. J Hepatol 2002;37:837-842.
34. Younossi ZM, McCullough AJ, Ong JP, Barnes DS, Post A, Tavill A, et al. Obesity and non-alcoholic fatty liver disease in chronic hepatitis C. J Clin Gastroenterol 2004;38:705-709.
35. Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilabert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. HEPATOLOGY 2006;43: 492-499.
36. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. HEPATOLOGY 2006;44:865-873.
37. Mayo M, Parks J, Huet B, Combes B, Mills SA, Markin R, et al. Serum fibrosis markers predict future clinical decompensation in primary biliary cirrhosis better than liver biopsy, bilirubin, or Mayo risk score [Abstract]. HEPATOLOGY 2006;44:630A.
38. Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology 1996;110:1107-1119.
39. Davis GL, Czaja AJ, Ludwig J. Development and prognosis of histologic cirrhosis in corticosteroid-treated hepatitis B surface antigen-negative chronic active hepatitis. Gastroenterology 1984;87:1222-1227.
40. Colletta C, Smirne C, Fabris C, Foscolo AM, Toniutto P, Rapetti R, et al. Regression of fibrosis among long-term responders to antiviral treatment for chronic viral hepatitis [Abstract]. HEPATOLOGY 2007;46:300A–301A.
41. Sanchez-Conde M, Berenguer J, Miralles P, Alvarez F, Carlos Lopez J, Cosin J, et al. Liver biopsy findings for HIV-infected patients with chronic hepatitis C and persistently normal levels of alanine aminotransferase. Clin Infect Dis 2006;43:640-644.
42. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006;130:231-264; quiz 214-237.
43. Verma S, Gunuwan B, Mendler M, Govindrajan S, Redeker A. Factors predicting relapse and poor outcome in type I autoimmune hepatitis: role of cirrhosis development, patterns of transaminases during remission and plasma cell activity in the liver biopsy. Am J Gastroenterol 2004;99:1510-1516.
44. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. HEPATOLOGY 2002;36:479-497.
45. Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology 2005;128:297-303.
46. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. HEPATOLOGY 2004;39:1147-1171.
47. Lok AS, McMahon BJ. Chronic Hepatitis B. HEPATOLOGY 2007;47:507-539.
48. Tavill AS. Diagnosis and management of hemochromatosis. HEPATOLOGY 2001;33:1321-1328.
49. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. HEPATOLOGY 2000;31:1005-1013.
50. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. HEPATOLOGY 2008;47:2089-2111.
51. Hay JE, Czaja AJ, Rakela J, Ludwig J. The nature of unexplained chronic aminotransferase elevations of a mild to moderate degree in asymptomatic patients. HEPATOLOGY 1989;9:193-197.
52. Sorbi D, McGill DB, Thistle JL, Therneau TM, Henry J, Lindor KD. An assessment of the role of liver biopsies in asymptomatic patients with chronic liver test abnormalities. Am J Gastroenterol 2000;95:3206-3210.
53. Skelly MM, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. J Hepatol 2001;35:195-199.
54. Talley NJ, Roth A, Woods J, Hench V. Diagnostic value of liver biopsy in alcoholic liver disease. J Clin Gastroenterol 1988;10:647-650.
55. Elphick DA, Dube AK, McFarlane E, Jones J, Gleeson D. Spectrum of liver histology in presumed decompensated alcoholic liver disease. Am J Gastroenterol 2007;102:780-788.
56. Byron D, Minuk GY. Clinical hepatology: profile of an urban, hospital-based practice. HEPATOLOGY 1996;24:813-815.
57. Greeve M, Ferrell L, Kim M, Combs C, Roberts J, Ascher N, et al. Cirrhosis of undefined pathogenesis: absence of evidence for unknown viruses or autoimmune processes. HEPATOLOGY 1993;17:593-598.
58. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. HEPATOLOGY 1990;11:74-80.
59. Abdelmalek M, Ludwig J, Lindor KD. Two cases from the spectrum of nonalcoholic steatohepatitis. J Clin Gastroenterol 1995;20:127-130.
60. Yoshioka Y, Hashimoto E, Yatsuji S, Kaneda H, Taniai M, Tokushige K, et al. Nonalcoholic steatohepatitis: cirrhosis, hepatocellular carcinoma, and burnt-out NASH. J Gastroenterol 2004;39:1215-1218.
61. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. HEPATOLOGY 1999;29:664-669.
62. Poonawala A, Nair SP, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. HEPATOLOGY 2000;32:689-692.
63. Kojima H, Sakurai S, Matsumura M, Umemoto N, Uemura M, Morimoto H, et al. Cryptogenic cirrhosis in the region where obesity is not prevalent. World J Gastroenterol 2006;12:2080-2085.
64. Berg T, Neuhaus R, Klein R, Leder K, Lobeck H, Bechstein WO, et al. Distinct enzyme profiles in patients with cryptogenic cirrhosis reflect heterogeneous causes with different outcomes after liver transplantation (OLT): a long-term documentation before and after OLT. Transplantation 2002;74:792-798.
65. Duclos-Vallee JC, Yilmaz F, Johanet C, Roque-Afonso AM, Gigou M, Trichet C, et al. Could post-liver transplantation course be helpful for the diagnosis of so called cryptogenic cirrhosis? Clin Transplant 2005;19: 591-599.
66. Contos MJ, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transpl 2001;7:363-373.
67. Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, et al. Cryptogenic cirrhosis: clinicopathologic findings at and after liver transplantation. Hum Pathol 2002;33:1098-1104.
68. Lee V, Kleiner DE, Al-Osaimi AMS, Argo CK, Northup PG, Berg CL, et al. Histological characteristics of patients with 'cryptogenic' cirrhosis and prior biopsy showing NASH [Abstract]. HEPATOLOGY 2007;46:742A.
69. Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, Czaja A, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. HEPATOLOGY 2006;44:489-501.
70. Smith AD. Recurrence of the original liver disease. In: Killenberg PG, Clavien PA, eds. Medical Care of the Liver Transplant Patient. 3rd ed. Oxford, UK: Blackwell; 2006:419-438.
71. Firpi RJ, Abdelmalek MF, Soldevila-Pico C, Cabrera R, Shuster JJ, Theriaque D, et al. One-year protocol liver biopsy can stratify fibrosis progression in liver transplant recipients with recurrent hepatitis C infection. Liver Transpl 2004;10:1240-1247.
72. Emiroglu R, Basaran O, Yagmurdur MC, Boyacioglu S, Bilezikci B, Haberal M. Liver biopsy is mandatory to choose suitable liver grafts. Transplant Proc 2003;35:2765-2767.
73. Adani GL, Baccarani U, Sainz-Barriga M, Lorenzin D, Bresadola V, Risaliti A, et al. The role of hepatic biopsy to detect macrovacuolar steatosis during liver procurement. Transplant Proc 2006;38:1404-1406.
74. Nadalin S, Malago M, Valentin-Gamazo C, Testa G, Baba HA, Liu C, et al. Preoperative donor liver biopsy for adult living donor liver transplantation: risks and benefits. Liver Transpl 2005;11:980-986.
75. Brancatelli G. Science to practice: should biopsy be performed in potential liver donors when unenhanced CT shows an unacceptable degree of steatosis for transplantation? Radiology 2006;239:1-2.
76. Savas N, Coskun M, Bilezikci B, Uruc I, Karakayali H, Yilmaz U, Haberal M. Value of an individual liver biopsy in the preoperative eval-

uation of apparently healthy potential liver donors. Liver Transpl 2008; 14:541-546.
77. Bruix J, Sherman M. Management of hepatocellular carcinoma. HEPATOLOGY 2005;42:1208-1236.
78. Stigliano R, Burroughs AK. Should we biopsy each liver mass suspicious for HCC before liver transplantation?–no, please don't. J Hepatol 2005; 43:563-568.
79. Marsh JW, Dvorchik I. Should we biopsy each liver mass suspicious for hepatocellular carcinoma before liver transplantation?–yes. J Hepatol 2005;43:558-562.
80. Saborido BP, Diaz JC, de Los Galanes SJ, Segurola CL, de Usera MA, Garrido MD, et al. Does preoperative fine needle aspiration-biopsy produce tumor recurrence in patients following liver transplantation for hepatocellular carcinoma? Transplant Proc 2005;37:3874-3877.
81. Chang S, Kim SH, Lim HK, Lee WJ, Choi D, Lim JH. Needle tract implantation after sonographically guided percutaneous biopsy of hepatocellular carcinoma: evaluation of doubling time, frequency, and features on CT. AJR Am J Roentgenol 2005;185:400-405.
82. Durand F, Regimbeau JM, Belghiti J, Sauvanet A, Vilgrain V, Terris B, et al. Assessment of the benefits and risks of percutaneous biopsy before surgical resection of hepatocellular carcinoma. J Hepatol 2001;35:254-258.
83. Liu YW, Chen CL, Chen YS, Wang CC, Wang SH, Lin CC. Needle tract implantation of hepatocellular carcinoma after fine needle biopsy. Dig Dis Sci 2007;52:228-231.
84. Van Kleek EJ, Schwartz JM, Rayhill SC, Rosen HR, Cotler SJ. Liver transplantation for hepatocellular carcinoma: a survey of practices. J Clin Gastroenterol 2006;40:643-647.
85. Perkins JD. To biopsy or not to biopsy? Liver Transpl 2006;12:885-886.
86. Pawlik TM, Gleisner AL, Anders RA, Assumpcao L, Maley W, Choti MA. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. Ann Surg 2007;245:435-442.
87. Seeto RK, Rockey DC. Pyogenic liver abscess. Changes in etiology, management, and outcome. Medicine (Baltimore) 1996;75:99-113.
88. Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion 2005;45:1413-1425.
89. Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. HEPATOLOGY 2006;44:1039-1046.
90. Tripodi A, Caldwell SH, Hoffman M, Trotter JF, Sanyal AJ. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. Aliment Pharmacol Ther 2007;26:141-148.
91. Tripodi A, Mannucci PM. Abnormalities of hemostasis in chronic liver disease: reappraisal of their clinical significance and need for clinical and laboratory research. J Hepatol 2007;46:727-733.
92. Leebeek FW, Kluft C, Knot EA, de Maat MP, Wilson JH. A shift in balance between profibrinolytic and antifibrinolytic factors causes enhanced fibrinolysis in cirrhosis. Gastroenterology 1991;101:1382-1390.
93. Hu KQ, Yu AS, Tiyyagura L, Redeker AG, Reynolds TB. Hyperfibrinolytic activity in hospitalized cirrhotic patients in a referral liver unit. Am J Gastroenterol 2001;96:1581-1586.
94. Xavier E, Park SH, May DS, Patrie J, Hespenheide EE, Northup PG, et al. Comparison of conventional tests with thromboelastography in assessing bleeding risk among decompensated cirrhosis patients [Abstract]. HEPATOLOGY 2007;46:588A.
95. Hittelet A, Deviere J. Management of anticoagulants before and after endoscopy. Can J Gastroenterol 2003;17:329-332.
96. Kane D, Veale DJ, FitzGerald O, Reece R. Survey of arthroscopy performed by rheumatologists. Rheumatology (Oxford) 2002;41:210-215.
97. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, et al. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. Gastrointest Endosc 2002;55:775-779.
98. Madura JA, Rookstool M, Wease G. The management of patients on chronic coumadin therapy undergoing subsequent surgical procedures. Am Surg 1994;60:542-546; discussion 546-547.
99. Ahmed A, Samuels SL, Keeffe EB, Cheung RC. Delayed fatal hemorrhage from pseudoaneurysm of the hepatic artery after percutaneous liver biopsy. Am J Gastroenterol 2001;96:233-237.
100. Ren FY, Piao XX, Jin AL. Delayed hemorrhage from hepatic artery after ultrasound-guided percutaneous liver biopsy: a case report. World J Gastroenterol 2006;12:4273-4275.
101. Caldwell SH. Controlling pain in liver biopsy, or "we will probably need to repeat the biopsy in a year or two to assess the response". Am J Gastroenterol 2001;96:1327-1329.
102. Eisenberg E, Konopniki M, Veitsman E, Kramskay R, Gaitini D, Baruch Y. Prevalence and characteristics of pain induced by percutaneous liver biopsy. Anesth Analg 2003;96:1392-1396, table of contents.
103. Perrault J, McGill DB, Ott BJ, Taylor WF. Liver biopsy: complications in 1000 inpatients and outpatients. Gastroenterology 1978;74:103-106.
104. Sherlock S, Dick R, Van Leeuwen DJ. Liver biopsy today. The Royal Free Hospital experience. J Hepatol 1985;1:75-85.
105. Lebrec D, Goldfarb G, Degott C, Rueff B, Benhamou JP. Transvenous liver biopsy: an experience based on 1000 hepatic tissue samplings with this procedure. Gastroenterology 1982;83:338-340.
106. Bull HJ, Gilmore IT, Bradley RD, Marigold JH, Thompson RP. Experience with transjugular liver biopsy. Gut 1983;24:1057-1060.
107. Orlando R, Lirussi F, Okolicsanyi L. Laparoscopy and liver biopsy: further evidence that the two procedures improve the diagnosis of liver cirrhosis. A retrospective study of 1,003 consecutive examinations. J Clin Gastroenterol 1990;12:47-52.
108. Poniachik J, Bernstein DE, Reddy KR, Jeffers LJ, Coelho-Little ME, Civantos F, et al. The role of laparoscopy in the diagnosis of cirrhosis. Gastrointest Endosc 1996;43:568-571.
109. Denzer U, Arnoldy A, Kanzler S, Galle PR, Dienes HP, Lohse AW. Prospective randomized comparison of minilaparoscopy and percutaneous liver biopsy: diagnosis of cirrhosis and complications. J Clin Gastroenterol 2007;41:103-110.
110. Steele K, Schweitzer MA, Lyn-Sue J, Kantsevoy SV. Flexible transgastric peritoneoscopy and liver biopsy: a feasibility study in human beings (with videos). Gastrointest Endosc 2008;68:61-66.
111. Riley SA, Ellis WR, Irving HC, Lintott DJ, Axon AT, Losowsky MS. Percutaneous liver biopsy with plugging of needle track: a safe method for use in patients with impaired coagulation. Lancet 1984;2:436.
112. Tobin MV, Gilmore IT. Plugged liver biopsy in patients with impaired coagulation. Dig Dis Sci 1989;34:13-15.
113. Fandrich CA, Davies RP, Hall PM. Small gauge gelfoam plug liver biopsy in high risk patients: safety and diagnostic value. Australas Radiol 1996; 40:230-234.
114. Sawyerr AM, McCormick PA, Tennyson GS, Chin J, Dick R, Scheuer PJ, et al. A comparison of transjugular and plugged-percutaneous liver biopsy in patients with impaired coagulation. J Hepatol 1993;17:81-85.
115. Sherman KE, Goodman ZD, Sullivan ST, Faris-Young S. Liver biopsy in cirrhotic patients. Am J Gastroenterol 2007;102:789-793.
116. Alexander JA, Smith BJ. Midazolam sedation for percutaneous liver biopsy. Dig Dis Sci 1993;38:2209-2211.
117. Castera L, Negre I, Samii K, Buffet C. Patient-administered nitrous oxide/oxygen inhalation provides safe and effective analgesia for percutaneous liver biopsy: a randomized placebo-controlled trial. Am J Gastroenterol 2001;96:1553-1557.
118. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. British Society of Gastroenterology. Gut 1999;45(Suppl 4): IV1-IV11.
119. Hyun CB, Beutel VJ. Prospective randomized trial of post-liver biopsy recovery positions: does positioning really matter? J Clin Gastroenterol 2005;39:328-332.
120. Firpi RJ, Soldevila-Pico C, Abdelmalek MF, Morelli G, Judah J, Nelson DR. Short recovery time after percutaneous liver biopsy: should we change our current practices? Clin Gastroenterol Hepatol 2005;3:926-929.

121. Beddy P, Lyburn I, Geoghegan T, Buckley O, Buckley A, Torreggiani W. Outpatient liver biopsy: a prospective evaluation of 500 cases. Gut 2007; 56:307.
122. Manolakopoulos S, Triantos C, Bethanis S, Theodoropoulos J, Vlachogiannakos J, Cholongitas E, et al. Ultrasound-guided liver biopsy in real life: comparison of same-day prebiopsy versus real-time ultrasound approach. J Gastroenterol Hepatol 2007;22:1490-1493.
123. Lindor KD, Bru C, Jorgensen RA, Rakela J, Bordas JM, Gross JB, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. HEPATOLOGY 1996;23:1079-1083.
124. Stone MA, Mayberry JF. An audit of ultrasound guided liver biopsies: a need for evidence-based practice. Hepatogastroenterology 1996;43:432-434.
125. Farrell RJ, Smiddy PF, Pilkington RM, Tobin AA, Mooney EE, Temperley IJ, et al. Guided versus blind liver biopsy for chronic hepatitis C: clinical benefits and costs. J Hepatol 1999;30:580-587.
126. Younossi ZM, Teran JC, Ganiats TG, Carey WD. Ultrasound-guided liver biopsy for parenchymal liver disease: an economic analysis. Dig Dis Sci 1998;43:46-50.
127. Pasha T, Gabriel S, Therneau T, Dickson ER, Lindor KD. Cost-effectiveness of ultrasound-guided liver biopsy. HEPATOLOGY 1998;27:1220-1226.
128. Riley TR 3rd. How often does ultrasound marking change the liver biopsy site? Am J Gastroenterol 1999;94:3320-3322.
129. Muir AJ, Trotter JF. A survey of current liver biopsy practice patterns. J Clin Gastroenterol 2002;35:86-88.
130. Mayoral W, Lewis JH. Percutaneous liver biopsy: what is the current approach? Results of a questionnaire survey. Dig Dis Sci 2001;46:118-127.
131. Little AF, Ferris JV, Dodd GD 3rd, Baron RL. Image-guided percutaneous hepatic biopsy: effect of ascites on the complication rate. Radiology 1996;199:79-83.
132. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology 1990;99:1396-1400.
133. Bialecki ES, Ezenekwe AM, Brunt EM, Collins BT, Ponder TB, Bieneman BK, et al. Comparison of liver biopsy and noninvasive methods for diagnosis of hepatocellular carcinoma. Clin Gastroenterol Hepatol 2006; 4:361-368.
134. Tung WC, Huang YJ, Leung SW, Kuo FY, Tung HD, Wang JH, et al. Incidence of needle tract seeding and responses of soft tissue metastasis by hepatocellular carcinoma postradiotherapy. Liver Int 2007;27:192-200.
135. Maturen KE, Nghiem HV, Marrero JA, Hussain HK, Higgins EG, Fox GA, et al. Lack of tumor seeding of hepatocellular carcinoma after percutaneous needle biopsy using coaxial cutting needle technique. AJR Am J Roentgenol 2006;187:1184-1187.
136. Khuroo MS, Wani NA, Javid G, Khan BA, Yattoo GN, Shah AH, et al. Percutaneous drainage compared with surgery for hepatic hydatid cysts. N Engl J Med 1997;337:881-887.
137. Ewe K. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. Dig Dis Sci 1981;26:388-393.
138. Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, et al. Thrombin generation in patients with cirrhosis: the role of platelets. HEPATOLOGY 2006;44:440-445.
139. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and Model for End-Stage Liver Disease (MELD) based on selection of clinical laboratory. Am J Transpl 2007;7:1624-1628.
140. Sharma P, McDonald GB, Banaji M. The risk of bleeding after percutaneous liver biopsy: relation to platelet count. J Clin Gastroenterol 1982; 4:451-453.
141. Bonnard P, Vitte RL, Barbare JC, Denis J, Stepani P, Di Martino V, et al. Is bleeding time measurement useful for choosing the liver biopsy route? The results of a pragmatic, prospective multicentric study in 219 patients. J Clin Gastroenterol 1999;29:347-349.
142. Boberg KM, Brosstad F, Egeland T, Egge T, Schrumpf E. Is a prolonged bleeding time associated with an increased risk of hemorrhage after liver biopsy? Thromb Haemost 1999;81:378-381.
143. Pawa S, Ehrinpreis M, Mutchnick M, Janisse J, Dhar R, Siddiqui FA. Percutaneous liver biopsy is safe in chronic hepatitis C patients with end-stage renal disease. Clin Gastroenterol Hepatol 2007;5:1316-1320.
144. Colucci M, Binetti BM, Branca MG, Clerici C, Morelli A, Semeraro N, et al. Deficiency of thrombin activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. HEPATOLOGY 2003;38: 230-237.
145. McVay PA, Toy PT. Lack of increased bleeding after liver biopsy in patients with mild hemostatic abnormalities. Am J Clin Pathol 1990;94: 747-753.
146. Dillon JF, Simpson KJ, Hayes PC. Liver biopsy bleeding time: an unpredictable event. J Gastroenterol Hepatol 1994;9:269-271.
147. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut 1995;36: 437-441.
148. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol 2004;126:139-152.
149. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion 2006;46:1279-1285.
150. Triulzi DJ. The art of plasma transfusion therapy. Transfusion 2006;46: 1268-1270.
151. Jeffers L, Chalasani N, Balart L, Pyrsopoulos N, Erhardtsen E. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. Gastroenterology 2002; 123:118-126.
152. Bellest L, Eschwege V, Poupon R, Chazouilleres O, Robert A. A modified international normalized ratio as an effective way of prothrombin time standardization in hepatology. HEPATOLOGY 2007;46:528-534.
153. Tripodi A, Chantarangkul V, Primignani M, Fabris F, Dell'Era A, Sei C, et al. The international normalized ratio calibrated for cirrhosis (INR-(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. HEPATOLOGY 2007;46:520-527.
154. Tripodi A, Chantarangkul V, Mannucci PM. The international normalized ratio to prioritize patients for liver transplantation: problems and possible solutions. J Thromb Haemost 2008;6:243-248.
155. Konkle BA, Nemo GJ. Defining effective therapies in transfusion medicine and hemostasis: new opportunities with the TMH Network. Transfusion 2005;45:1404-1406.
156. McMahon C, Pilkington R, Shea EO, Kelleher D, Smith OP. Liver biopsy in Irish hepatitis C-infected patients with inherited bleeding disorders. Br J Haematol 2000;109:354-359.
157. Wong VS, Baglin T, Beacham E, Wight DD, Petrik J, Alexander GJ. The role for liver biopsy in haemophiliacs infected with the hepatitis C virus. Br J Haematol 1997;97:343-347.
158. Theodore D, Fried MW, Kleiner DE, Kroner BL, Goedert JJ, Eyster ME, et al. Liver biopsy in patients with inherited disorders of coagulation and chronic hepatitis C. Haemophilia 2004;10:413-421.
159. Shin JL, Teitel J, Swain MG, Bain VG, Adams PC, Croitoru K, et al. A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with congenital bleeding disorders and hepatitis C: is it safe and useful? Am J Hematol 2005;78:85-93.
160. Zakaria N, Knisely A, Portmann B, Mieli-Vergani G, Wendon J, Arya R, et al. Acute sickle cell hepatopathy represents a potential contraindication for percutaneous liver biopsy. Blood 2003;101:101-103.
161. Tan KT, Rajan DK, Kachura JR, Hayeems E, Simons ME, Ho CS. Pain after percutaneous liver biopsy for diffuse hepatic disease: a randomized trial comparing subcostal and intercostal approaches. J Vasc Interv Radiol 2005;16:1215-1219.

162. Riley TR 3rd. Predictors of pain medication use after percutaneous liver biopsy. Dig Dis Sci 2002;47:2151-2153.
163. Akay S, Karasu Z, Noyan A, Pala S, Musoglu A, Ilter T, et al. Liver biopsy: is the pain for real or is it only the fear of it? Dig Dis Sci 2007;52:579-581.
164. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. Ann Intern Med 1993;118:96-98.
165. Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. J Hepatol 1986;2:165-173.
166. Huang JF, Hsieh MY, Dai CY, Hou NJ, Lee LP, Lin ZY, et al. The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies. Gut 2007;56:736-737.
167. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). HEPATOLOGY 2000;32:477-481.
168. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. Liver Int 2008;28:705-712.
169. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495-500.
170. Knauer CM. Percutaneous biopsy of the liver as a procedure for outpatients. Gastroenterology 1978;74:101-102.
171. Reichert CM, Weisenthal LM, Klein HG. Delayed hemorrhage after percutaneous liver biopsy. J Clin Gastroenterol 1983;5:263-266.
172. Minuk GY, Sutherland LR, Wiseman DA, MacDonald FR, Ding DL. Prospective study of the incidence of ultrasound-detected intrahepatic and subcapsular hematomas in patients randomized to 6 or 24 hours of bed rest after percutaneous liver biopsy. Gastroenterology 1987;92:290-293.
173. Froehlich F, Lamy O, Fried M, Gonvers JJ. Practice and complications of liver biopsy. Results of a nationwide survey in Switzerland. Dig Dis Sci 1993;38:1480-1484.
174. Chuah SY, Moody GA, Wicks AC, Mayberry JF. A nationwide survey of liver biopsy–is there a need to increase resources, manpower and training? Hepatogastroenterology 1994;41:4-8.
175. Thampanitchawong P, Piratvisuth T. Liver biopsy:complications and risk factors. World J Gastroenterol 1999;5:301-304.
176. Sterling R, Plecha D, Post T, Herbener T, Haaga J. Increasing size of true cut needle is associated with increased bleeding in porcine liver biopsies [Abstract]. HEPATOLOGY 1995;22:694A.
177. Glaser J, Pausch J. Risk of liver biopsy [in German]. Z Gastroenterol 1996;34:XXII.
178. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. HEPATOLOGY 2005;41:553-558.
179. Sue M, Caldwell SH, Dickson RC, Macalindong C, Rourk RM, Charles C, et al. Variation between centers in technique and guidelines for liver biopsy. Liver 1996;16:267-270.
180. Kalambokis G, Manousou P, Vibhakorn S, Marelli L, Cholongitas E, Senzolo M, et al. Transjugular liver biopsy - Indications, adequacy, quality of specimens, and complications - A systematic review. J Hepatol 2007;47:284-294.
181. Remuzzi G. Bleeding in renal failure. Lancet 1988;1:1205-1208.
182. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. N Engl J Med 1983;308:8-12.
183. DiMichele DM, Hathaway WE. Use of DDAVP in inherited and acquired platelet dysfunction. Am J Hematol 1990;33:39-45.
184. Hanley JP, Jarvis LM, Andrews J, Dennis R, Lee R, Simmonds P, et al. Investigation of chronic hepatitis C infection in individuals with haemophilia: assessment of invasive and non-invasive methods. Br J Haematol 1996;94:159-165.
185. Bubak ME, Porayko MK, Krom RA, Wiesner RH. Complications of liver biopsy in liver transplant patients: increased sepsis associated with choledochojejunostomy. HEPATOLOGY 1991;14:1063-1065.
186. Kliewer MA, Sheafor DH, Paulson EK, Helsper RS, Hertzberg BS, Nelson RC. Percutaneous liver biopsy: a cost-benefit analysis comparing sonographic and CT guidance. AJR Am J Roentgenol 1999;173:1199-1202.
187. Rossi P, Sileri P, Gentileschi P, Sica GS, Forlini A, Stolfi VM, et al. Percutaneous liver biopsy using an ultrasound-guided subcostal route. Dig Dis Sci 2001;46:128-132.
188. Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol 2003;39:239-244.
189. Crawford AR, Lin XZ, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. HEPATOLOGY 1998;28:323-331.
190. Rocken C, Meier H, Klauck S, Wolff S, Malfertheiner P, Roessner A. Large-needle biopsy versus thin-needle biopsy in diagnostic pathology of liver diseases. Liver 2001;21:391-397.
191. Riley TR 3rd, Ruggiero FM. The effect of processing on liver biopsy core size. Dig Dis Sci 2008;53:2775-2777.
192. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005;128:1898-1906.
193. Holund B, Poulsen H, Schlichting P. Reproducibility of liver biopsy diagnosis in relation to the size of the specimen. Scand J Gastroenterol 1980;15:329-335.
194. Schiano TD, Azeem S, Bodian CA, Bodenheimer HC Jr, Merati S, Thung SN, et al. Importance of specimen size in accurate needle liver biopsy evaluation of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2005;3:930-935.
195. Abdi W, Millan JC, Mezey E. Sampling variability on percutaneous liver biopsy. Arch Intern Med 1979;139:667-669.
196. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618.
197. Colombo M, Del Ninno E, de Franchis R, De Fazio C, Festorazzi S, Ronchi G, et al. Ultrasound-assisted percutaneous liver biopsy: superiority of the Tru-Cut over the Menghini needle for diagnosis of cirrhosis. Gastroenterology 1988;95:487-489.
198. Brunetti E, Silini E, Pistorio A, Cavallero A, Marangio A, Bruno R, et al. Coarse vs. fine needle aspiration biopsy for the assessment of diffuse liver disease from hepatitis C virus-related chronic hepatitis. J Hepatol 2004;40:501-506.
199. Cholongitas E, Quaglia A, Samonakis D, Mela M, Patch D, Dhillon AP, et al. Transjugular liver biopsy in patients with diffuse liver disease: comparison of three cores with one or two cores for accurate histological interpretation. Liver Int 2007;27:646-653.
200. Brunt EM, Olynyk JK, Britton RS, Janney CG, Di Bisceglie AM, Bacon BR. Histological evaluation of iron in liver biopsies: relationship to HFE mutations. Am J Gastroenterol 2000;95:1788-1793.
201. Deugnier YM, Loreal O, Turlin B, Guyader D, Jouanolle H, Moirand R, et al. Liver pathology in genetic hemochromatosis: a review of 135 homozygous cases and their bioclinical correlations. Gastroenterology 1992;102:2050-2059.
202. Olynyk JK, O'Neill R, Britton RS, Bacon BR. Determination of hepatic iron concentration in fresh and paraffin-embedded tissue: diagnostic implications. Gastroenterology 1994;106:674-677.
203. Bejarano PA, Koehler A, Sherman KE. Second opinion pathology in liver biopsy interpretation. Am J Gastroenterol 2001;96:3158-3164.
204. Hahm GK, Niemann TH, Lucas JG, Frankel WL. The value of second opinion in gastrointestinal and liver pathology. Arch Pathol Lab Med 2001;125:736-739.
205. Tomaszewski JE, Bear HD, Connally JA, Epstein JI, Feldman M, Foucar K, et al. Consensus conference on second opinions in diagnos-

tic anatomic pathology. Who, what, and when. Am J Clin Pathol 2000;114:329-335.
206. Crawford JM. Evidence-based interpretation of liver biopsies. Lab Invest 2006;86:326-334.
207. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. HEPATOLOGY 1981;1:431-435.
208. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22: 696-699.
209. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. HEPATOLOGY 2005;41: 1313-1321.
210. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. HEPATOLOGY 1994;19:1513-1520.
211. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol 1995;19:1409-1417.
212. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. HEPATOLOGY 1996;24:289-293.
213. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. HEPATOLOGY 2005;41: 48-54.
214. Nobili V, Comparcola D, Sartorelli MR, Natali G, Monti L, Falappa P, et al. Blind and ultrasound-guided percutaneous liver biopsy in children. Pediatr Radiol 2003;33:772-775.