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Needle Biopsy in Children With Liver Diseases

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1. Introduction

The diagnosis of most liver diseases in children requires histological confirmation, thus liver biopsies are routine procedures in specialist centre. Although sensitive and relatively accurate blood tests used to detect and diagnose liver disease have now become widely available, percutaneous needle biopsy provides the histopathological examination and assessment of liver disease and remains the cornerstone in the evaluation and management of parenchymal liver diseases [1–5]. Paul Ehrlich is credited with performing the first percutaneous liver biopsy in 1883 in Germany. However, the technique required up to a 15-minute intrahepatic phase, making it impractical and probably unsafe. In 1958, Menghini reported a new technique, which became more widely used [5, 6]. Historically liver biopsy was used exclusively for adult patients, just in the last 50 years, following the developing knowledge in pediatric hepatology, it has taken on an important role in the clinical practice. In the past and even today many authors, discuss about when liver biopsy is recommended, regarding indications and timing.

2. Indications for liver biopsy in children overview

Actually numerous studies strongly suggest that due to the limitations and risks of biopsy, as well as the improvement of the diagnostic accuracy of new noninvasive biomarkers (Fibroscan, FibroTest, ELF) (7-14), liver biopsy should no longer be considered mandatory as a first line estimate of fibrosis in the most frequent chronic liver diseases. In reality even if the development of non-invasive markers of liver injury must be encouraged especially for the assessment of liver fibrosis, the consensus in many conference statements recommend liver biopsy for the diagnosis and the management of almost all patients with liver diseases (15-18).

To date liver biopsy has three major roles: for diagnosis, for assessment of prognosis (disease staging), and/ or to assist in making therapeutic management decisions.

As said, when to order a liver biopsy is a subject of contention in the medical community especially whether deciding to recommend a liver biopsy in a child.

Nearly all doctors agree that a liver biopsy should routinely ordered when tests reveal raised liver enzyme over several months. The liver enzyme elevation that merits a histological evaluation can range from 1.5 times to twice the normal range for a child of that weight and age. Considering the chronic trend of altered liver enzymes (almost 6 months) as one of the major indication, instead the acute flares of elevated enzymesin children often end to find a spontaneously resolution being related to some infections, fever or medical treatments.Diseases and situations in which liver biopsy may be indicated are listed in Tables 1. It is essential to have information about liver size and consistency and the presence of cyst or dilatated bile ducts from ultrasound, and if necessary to have a "spot"marked on the abdomento ensure an accurate biopsy. Correct information about coagulation parameters is crucial. Prothrombin time should be within 3 s of control values; platelets > 80.000/ L. The patient's blood group should be known, and it is prudent to cross-match a unit of blood prior to the procedure.However even when present an indication, liver biopsy could be difficult to perform because of clinical conditions of the patient. Abnormal coagulationis the main contraindications while in presence of ascitis different techniques other than the needle aspiration should be considered (table 2). In these cases when liver biopsy is strictly necessary alternative techniques will be used, such as transjugular biopsy and the procedure should be performed in high experienced centre (19-20).

2.1 Use of liver biopsy in specific disease

Neonatal cholestasis is a relevant condition in which liver biopsy play a pivotal role and has to be considered as soon as possible to provide specific treatment. In case of biliary atresia early diagnosis in vital, as the Kasai portoenterostomy is less likely to be successful the later is performed. Biliary atresia is the cause of liver disease in approximately 25% on infants presenting with neonatal cholestasis and percutaneous liver biopsy is essential and has high diagnostic specificity. Features of bile duct obstruction (duct reaction, previously known as ductular proliferation; bile plugs; portal tract edema) are usually obvious along with variable fibrosis and giant cell transformation (Figure 1). However the earlier the liver biopsy is performed, the more difficult it may be to interpret. 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. The liver biopsy plays a pivotal role in the follow-up of liver transplant (OLT). Pediatric liver transplant recipients often need to undergo liver biopsies for the detection and specification of complications such as acute or chronic graft rejection, infection, or drug toxicity. It is always necessary to have an histological confirmation (mixed inflammatory infiltrate in the portal tract with subendothelial lymphoid infiltration) (Figure 2). 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 (21-23).Nevertheless when the medical history, physical examination, biochemical, serological, or imaging investigation have shown the presence of specific markers liver biopsy should be brought forward to ruled out liver diseases that need to be treated such as Wilson disease or autoimmune hepatitis (figure 3) or to make a diagnosis of non alcoholic steatohepatitis (figure 4).

Neonatal cholestatic jaundice
Abnormal liver tests of unknown etiology
Focal of diffuse abnormalities on imaging studies
Need of liver tissue to further analisys (Wilson disease, metabolic disorders)
Prognosis—Staging of known parenchymal liver disease
Management—Developing treatment plans based on histologic analysis
Suspicion of inherited metabolic liver disease
Suspicion of autoimmune liver disease
Liver transplant follow up

Table 1. Indications for liver biopsy in children

Absolute
Severe coagulopathy (INR > 1,5, PLT < 50.000 mm^3)*
Possible vascular lesion
Treatment with FANS in the last week
Impossibility of blood transfusion, if necessary
Relative
Ascites
Obesity
Hemophilia*
* possible in some cases with blood products transfusion

Table 2. Contraindications to percutaneousliver biopsy in children

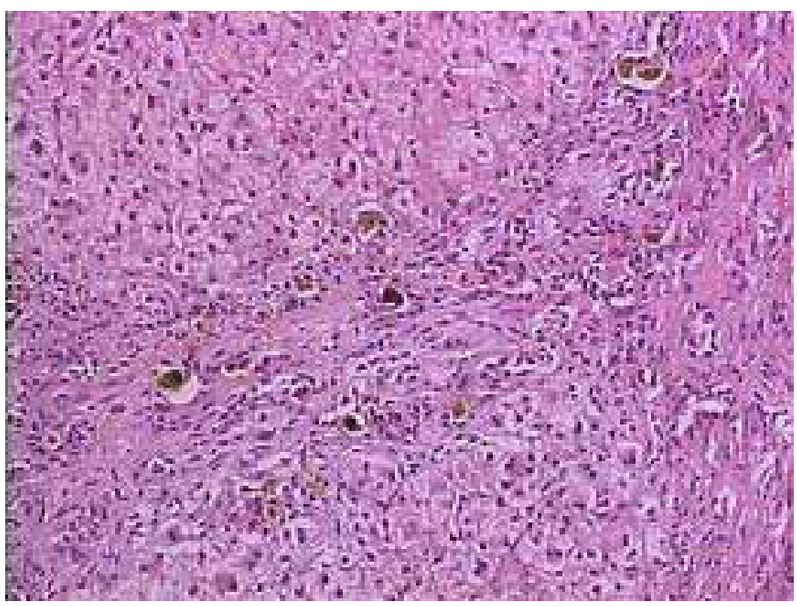

Fig. 1. Liver histology of a patient with biliary atresia

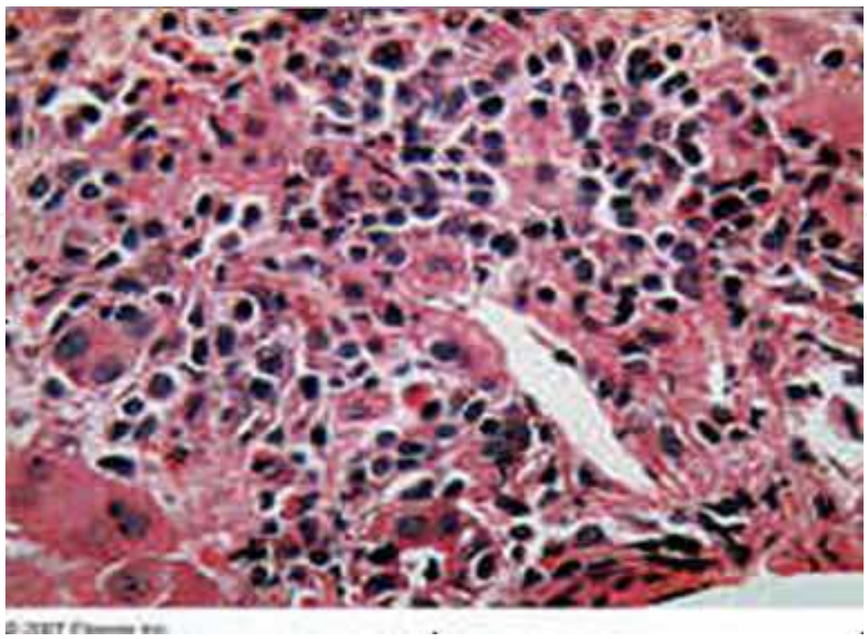

Fig. 2. Liver transplant histology showing acute showing expansion of portal spaces, due to ductular rejection proliferation, bile plugging in bile ductules and giant cells

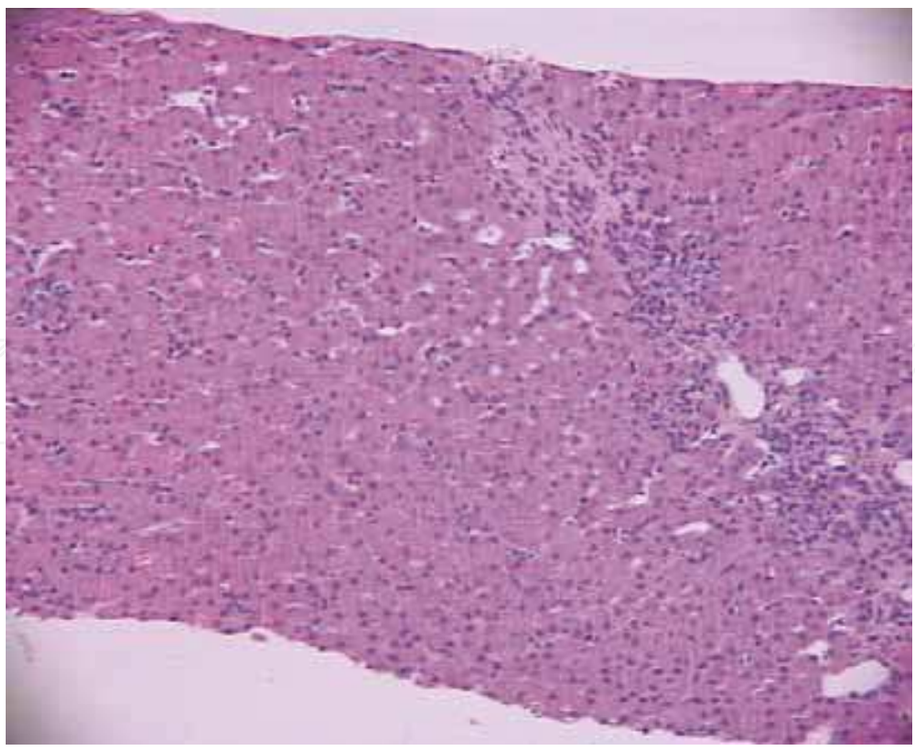

Fig. 3. Histology of an autoimmune hepatitis, portal

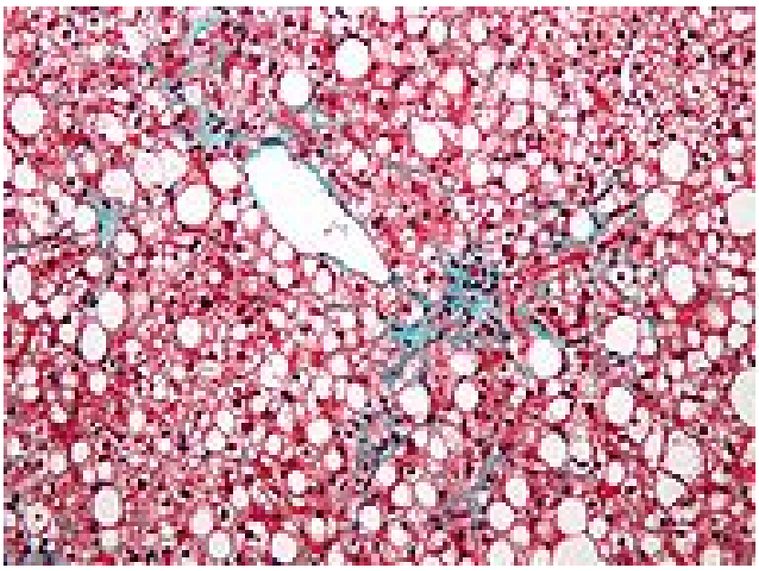

Fig. 4. Liver histology in a children with non alcoholic and peryportal lymphoplasmocityc infiltrate steatohepatitis

2.2 Risks and complications

Liver biopsy is generally regarded as a safe procedure, but an aspiration technique using a Menghini needle has a complication risk 1: 1000, while mortality rates up to 1:10,000 have been reported (24). The risks related to any procedure should always be balanced against potential benefits, and this is particularly pertinent in relation to children. Paediatric studies suggest an overall complication rate for percutaneous biopsy of 0.- 6.83% (2.4 – 4.5% major complications) (25-28). The data is difficult to compare between series as authors vary in their definition of major and minor complications, and in the exclusion criteria they employ. Complications include intraperitoneal haemorrhage, biliary peritonitis, haemobilia and injury to the duodenum, colon or lung. The risk of significant bleeding after an image-guided percutaneous liver biopsy, as measured by a decrease in haematocrit, is reported to be up to 3%. Paediatric studies have shown that the risk of complications is greater in patients with malignant disease, cirrhosis or recent bone marrow. It may be that these children should always be considered for a transjugular biopsy approach. Tumour seeding along the biopsy track remains a significant concern but unlike in hepatocellular carcinoma in the adult population, is rare in the commoner paediatric lesions such as hepatoblastoma. Smaller risks include lack of an adequate sample. With good operative technique, post-operative pain should be minimal, and post-operative infection rare. It is important to remember that sick children may deteriorate for clinical reasons unrelated to the liver biopsy itself. In table 3 are listed the rates of complications after needle biopsy as reported by D'Antiga and Mieli Vergani (29). The majority of complications occur in the first 3 hours after liver biopsy (30-35).

The complications of this potentially dangerous procedures are much reduced if performed in experts hands in specialized units under controlled conditions. Especially for children is crucial a well established post procedure observation to early recognize possible complications. (tab 4)

Complications	Rate %
Pain	0.056-22
Intraperitoneal haemorrhage	0.03-0.7
Intrahepatic bleeding	0.059-23
biliary peritonitis	0.03-0.22
haemobilia	0.059-0.2
Lung injury	0.08-0.28
Anhestetic reaction	0.029
Death	0.0083-0.03

Table 3. Rate of complications after liver biopsy. From D'antiga L and Mi Vergani G in Training and Educational corner, Bollettino Sigemp, 2010.

Blood pressure, pulse, respiration and temperature
15 min for 2h
30 min for 2h
Hourly for 2h
4 hourly as required
Chest X-rat/ abdominal ultrasound may be required if bleeding if suspected

Table 4. Post liver biopsy observation

3. Liver biopsy procedure

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 5).

The liver biopsy should be performed in a dedicated area, with adequate space for the operator, assistants, emergency equipment if necessary, or for family members during recovery.

All liver biopsy techniques require specific training so as to ensure appropriate-sized specimen retrieval and the lowest rate of complications. The main techniques are listed below:

- Percutaneous or needle biopsy
- Laparoscopic or open biopsy
- Transjugular biopsy

Percutanous Biopsy. This method may be undertaken in three different ways, namely palpation/ percussionguided, image-guided, and real-time image-guided. A palpation/ percussion-guided transthoracic approach, after infiltration of local anesthesia, is the classic percutaneous method. An aspiration technique with Menghini needle (or disposable variant) has a complication risk of 1 in 1000 biopsies. In fibrotic or chirrotic liver a Tru-Cut needle, which removes a larger core, may be necessary (Fig 5). The entry site is marked on the skin surface and the area is prepared and draped in sterile fashion. Local anesthetic is injected on the entry site.

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

Table 5. Liver Biopsy Terminology. From AASLD POSITION PAPER. Liver biopsy.2009

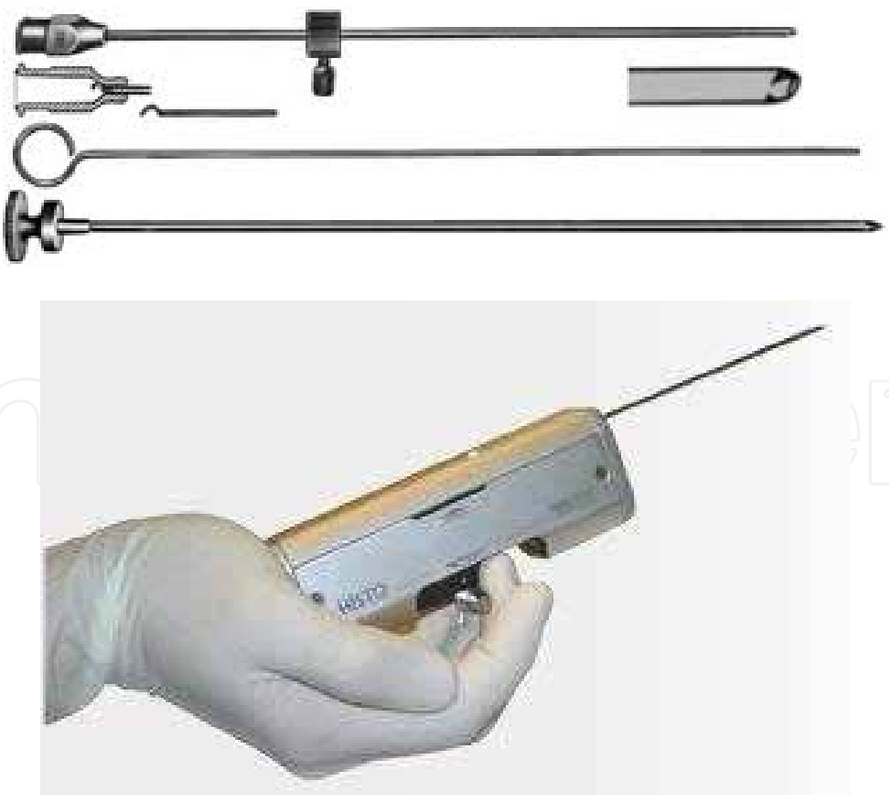

Fig. 5. Menghini needle set (on the top), Tru-cut automatic needle (below)

The transthoracic approach with the routine use of ultrasound scan (US) as a guide to liver biopsy seems to be associated with reduced rate of complications and provides a higher diagnostic yield. Indeed in pediatric liver biopsies and aspirations, US is preferred as a guidance method over CT scan for its versatility, ability to image in real time, decreased cost, portability, and lack of ionizing radiation (36). In spite of the above evidence, some authors question the advantages of a real-time US-guided approach versus blinded biopsy in relation to pain, hypotension, bleeding and rate of subsequent hospitalization (37). Moreover the number of passes should limited to three or fewer whenever possible otherwise the risk of bleeding is higher.

Surgical / laparoscopyc Biopsy. In some circumstances, a surgical 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. This technique of 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. Indeed a typical surgical approach (laparoscopic or open biopsy) for children is considered in case of suspected inherited metabolic liver disease in which more liver tissue is requested for molecular analysis and also muscle and skin biopsies are expected to reach a diagnosis.

Beyond all the different techniques and in order to justify the 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 thebiopsy 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 almost 10 for adult patients (38). However it's clear as the sampling variability is almost inevitable due to the patchy distribution of the disease especially in children(39). The size of specimen is essential especially to detect bile ducts or metabolic liver disease whereas less than 10 portal tracts could be enough to allow a diagnosis for viral hepatitis. Biopsy specimen should be obtained for routine histopatology, microbiology, electron microscopy, immunohistochemistry, and copper (if appropriate), and snap-frozen in liquid nitrogen for enzymatic or metabolic investigations. The interpretation of the histology may be difficult and requires considerable specialist expertise.

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; morbid obesity with a difficult-to-identify flank site; or those in whom free and wedged hepatic vein pressure measurements are additionally being sought, should be considered candidates to undergo liver biopsy by the transvenous route. Expertise is also important variableswhen considering transvenous biopsy.

The technique has been well described in the literature and should be considered standard for adult patients (40-43) while is not routinely performed for children, therefore availability of local expertise is extremely important when considering transvenous biopsy. Hanafee and collegues first performed transjugular biopsy in 1967. Since that time the technique has been shown to be safe and effective in adults and children.In 1998

Bergey et al demonstrated that specimens of diagnostic quality could be obtained in children of all ages and sizes, even small infants (44). The theory behind transjugular liver biopsy is that instead of making a hole in liver capsule that can bleed externally, the hole is made in the wall of hepatic vein and any bleeding is internal, back to the vein. The risk of bleeding occurs only if somehow the anterior the anterior capsule of the liver is punctured during the transjugular biopsy, which can occur if the liver is small or the needle is placed too pheripherally.

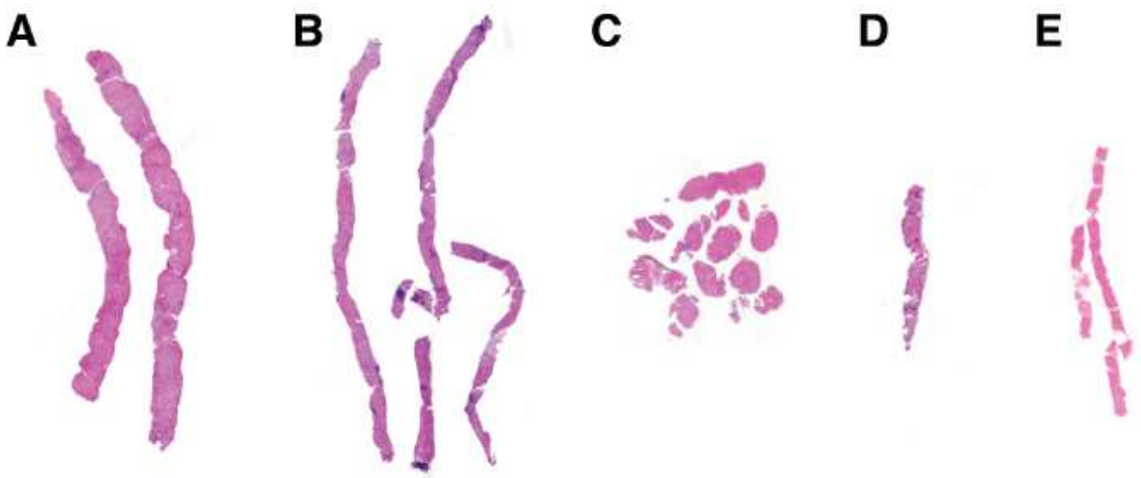

Fig. 6. Specimen of Liver obtained with needles and different techniques. All five biopsies shown in this figure were submitted for grading and staging of chronic hepatitis C. However, only (A) and (B) are felt to provide enough tissue for adequate histologic analysis. (C) is a fragmented specimen. (E) is a biopsy specimen 1.5 cm obtained with a 20-gauge needle. From AASLD POSITION PAPER. Liver biopsy.2009

4. Conclusion

The use of liver biopsy to obtain tissue for histological interpretation play a pivotal role in 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.

In terms of safety and comfort, it appears that the ultrasound guided approach 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.

Perhaps the use of non-invasive markers will be used in the future. For now, liver biopsy is useful andnecessary for the evaluation of chronic hepatopathies, despite the fact that it is not a perfect test.

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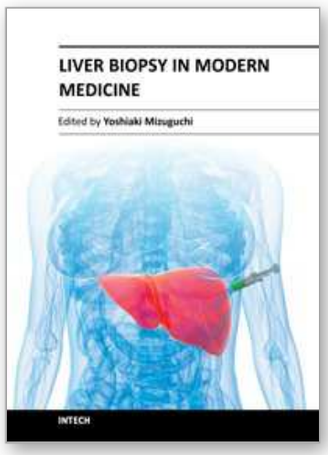

Liver Biopsy in Modern Medicine

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Liver biopsy, first performed by Paul Ehrlich in 1883, remains an important diagnostic procedure for the management of hepatobiliary disorders and the candidate/donated organ for transplantation. The book "Liver biopsy in Modern Medicine" comprises 21 chapters covering the various aspects of the biopsy procedure in detail and provides an up-to-date insightful coverage to the recent advances in the management of the various disorders with liver biospy. This book will keep up with cutting edge understanding of liver biopsy to many clinicians, physicians, scientists, pharmaceutics, engineers and other experts in a wide variety of different disciplines.

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