World Gastroenterology Organisation Global Guidelines

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

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INTRODUCTION

Over the past couple of decades, it has become increasingly clear that nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are now the number 1 cause of liver disease in the western countries. The prevalence of NAFLD has doubled during last 20 years, whereas the prevalence of other chronic liver diseases has remained stable or even decreased. More recent data confirm that NAFLD and NASH play an equally important role in the Middle East, Far East, Africa, the Caribbean, and Latin America.

NAFLD is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver. A subgroup of NAFLD patients displays liver cell injury and inflammation in addition to excessive fat (steatohepatitis). The latter condition, designated NASH, is virtually indistinguishable histologically from alcoholic steatohepatitis. While the simple steatosis of NAFLD does not correlate with increased short-term morbidity or mortality, progression of this condition to that of NASH dramatically increases the risks of cirrhosis, liver failure, and hepatocellular carcinoma.

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The authors declare that they have nothing to disclose.

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The exact cause of NASH has not been elucidated, and it is almost certainly not the same in every patient. Although it is most closely related to insulin resistance, obesity, and the metabolic syndrome, not all patients with these conditions have NAFLD/NASH, and not all patients with NAFLD/NASH suffer from one of these conditions. NASH is a potentially fatal condition, leading to cirrhosis, liver failure, and hepatocellular carcinoma.

There is no established therapy and there are no evidence-based clinical guidelines. There have not been any adequate prospective, double-blind, controlled trials to provide the data necessary to create an evidence-based guideline. This Global Guideline is intended to provide the best opinions of a group of experts from all areas of the globe concerning every aspect of this problem and the best approaches to diagnosing and treating this condition, taking locally available resources into account.

Cascades: A Resource-sensitive Approach

A gold-standard approach is feasible for regions and countries in which the full scale of diagnostic tests and medical treatment options are available for the management of NASH. However, such resources are not available throughout much of the world. With their

diagnostic and treatment cascades, the World Gastroenterology Organisation guidelines provide a resource-sensitive approach.

Cascade: a hierarchical set of diagnostic, therapeutic, and management options to deal with risk and disease, ranked by the resources available.

EPIDEMIOLOGY

NASH is an increasingly common chronic liver disease with worldwide distribution that is closely associated with diabetes and obesity, which have both reached epidemic proportions. It is estimated that there are at least 1.46 billion obese adults worldwide. Approximately 6 million individuals in the USA are estimated to have progressed to NASH and some 600,000 to NASH-related cirrhosis. There are significant cultural and geographic differences in the prevalence of obesity.

Whereas in most western countries, the preferred body image, especially in women, is very thin with minimal body fat, which is not necessarily true globally. In many other cultures, obesity is considered desirable and also regarded as a distinct sign of prosperity. In the USA, obesity is particularly epidemic in those from lower socioeconomic groups who rely heavily on diets provided by high-fat, high-calorie fast food outlets (junk food). The opposite is true in many poorer countries, where it is the well-to-do, better-educated population that has the highest prevalence of obesity (Table 1).

DIAGNOSIS

Diagnostic Strategy for NASH

NASH represents the most severe histologic form of NAFLD, which is defined by fat accumulation in the liver exceeding 5% of its weight. Uniform criteria for diagnosing and staging NASH are still debated.

Insulin resistance is related to obesity and is central to the pathogenesis of NAFLD. In addition, oxidative stress and cytokines are important contributing factors, together resulting in steatosis and progressive liver damage in genetically susceptible individuals.

The disease can remain asymptomatic for years, or can progress to cirrhosis and hepatocellular carcinoma.

Triggers for considering a diagnosis of NASH and starting testing of liver enzymes are: hypertension, type 2 diabetes, sleep apnea, a positive family history, nonblack ethnicity, obesity, hyperlipidemia, and a sedentary lifestyle (Figs. 1–3).

None of the noninvasive tests will rule out other possible underlying diseases or stage the disease for prognostic purposes.

Ultimately, NAFLD/NASH is a diagnosis of exclusion, and liver biopsy will often be required to confirm the diagnosis, stage the disease, rule out other liver diseases, and determine the need for and urgency of aggressive therapy.

Cascade: Options for Diagnosis in Patients With Suspected NAFLD/NASH

See Table 2.

TABLE 1. Estimated Prevalences of NAFLD and NASH

Regions	Population Studied	Prevalence of NAFLD in These Populations (%)
USA	Pediatric population	13-14
	General population	27-34
	Morbid obesity	75-92
	European Americans	33
	Hispanic Americans	45
	African Americans	24
Europe	Pediatric population	2.6-10
	General population	20-30
Western countries	General population	20-40
	Obesity or diabetes	75
	Morbid obesity	90-95
Worldwide	Obese population	40-90
Middle East	General population	20-30
Far East	General population	15
Pakistan	General population	18

Population With NAFLD Studied	Prevalence of NASH in These Populations (%)
Selected healthy liver donors	3-16
No inflammation or fibrosis	5
General population	10-20
High-risk, severe obesity	37
Patients at tertiary care centers	40-55

Reports on the prevalence of NAFLD and NASH vary substantially due to varying definitions, differences in the populations studied, and the diagnostic methods used.

NAFLD indicates nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

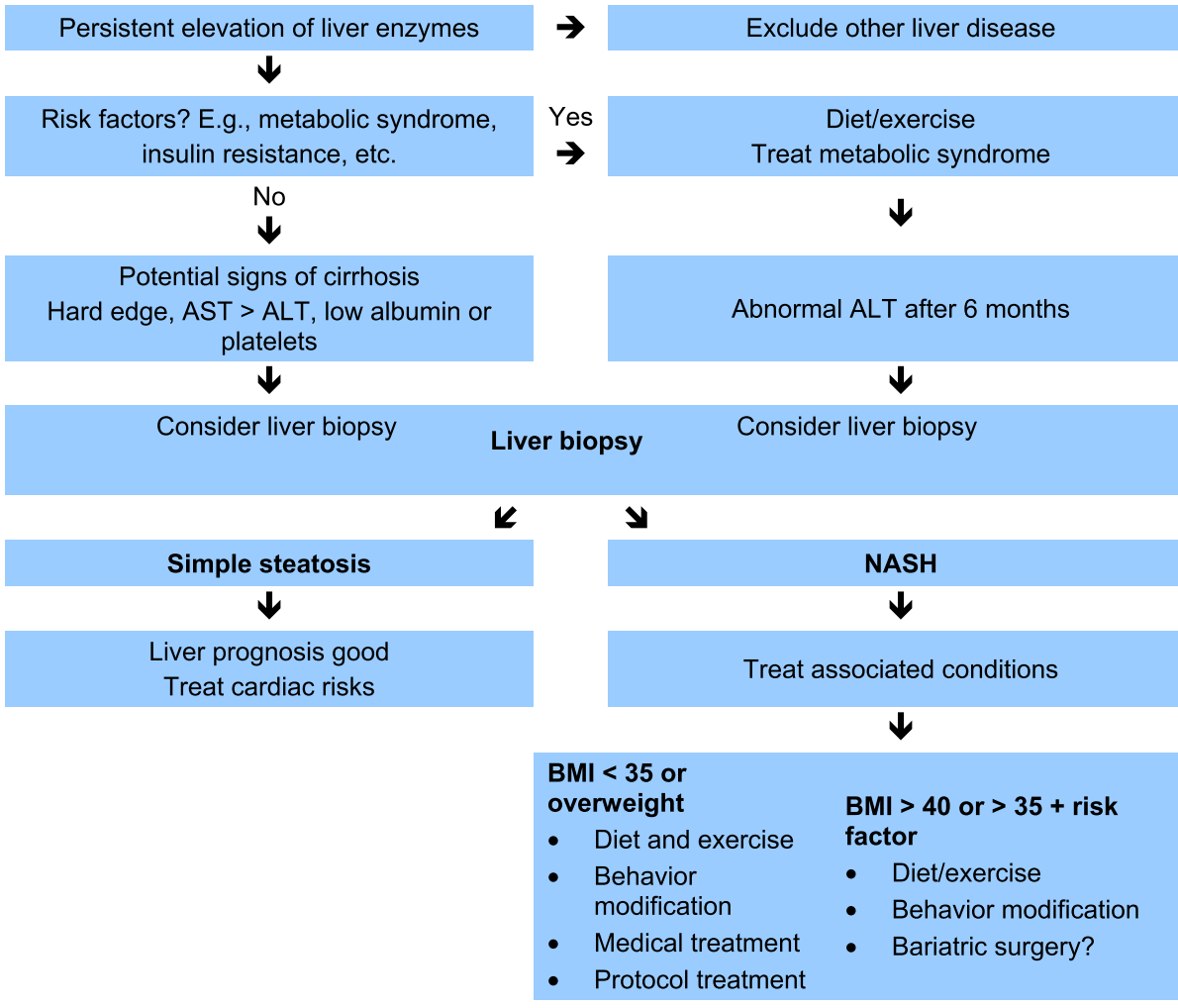

FIGURE 1. Management algorithm for nonalcoholic fatty liver disease. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index. Based on Rafiq and Younossi.[10] full color online

MANAGEMENT

Treatment Options for NASH

Treatment of Metabolic Conditions

Proper control of diabetes, hyperlipidemia, and cardiovascular risks is recommended. Studies with atorvastatin and pravastatin have shown improvement in histology in patients with NASH. NAFLD patients with dyslipidemia should be treated with statins. Patients with underlying liver disease do not seem to have any additional risk of statin toxicity. Serious hepatotoxicity from statins is rare.

> At the present time, there is no evidence-based approved drug therapy for NAFLD/NASH.

Improving Insulin Sensitivity: Weight Reduction

> Lifestyle change is critical in any attempt to reverse the course of NAFLD/NASH.

- *Diet:* A weight loss of 5% to 10% should be aimed for, and a 25% decrease in calories from the normal diet (ca. 2500 calories/d) for the patient's age and sex. A moderately calorie-restricted diet with modified macronutrient composition produces better results in comparison with a very low-caloric diet. Attention should be given to the role of a hypocaloric diet and counseling about the type of foods to be consumed—avoiding fructose and trans-fats present in soft drinks and fast foods, and increasing omega-3/omega-6 polyunsaturated fatty acids in diet. This may be difficult for the patient to adhere to, and many patients regain weight after an initial loss.
- *Exercise:* A moderate exercise program 3 to 4 times a week should be encouraged to achieve a heart rate of 60% to 75% of the age-based maximum.
- The efficacy of dietary and exercise measures should be assessed after a 6-month period; if they have been ineffective, additional therapeutic options such as pharmacologic therapy may then be considered.
- *Weight loss (bariatric) surgery* may be beneficial for patients with morbid obesity; again, this should be

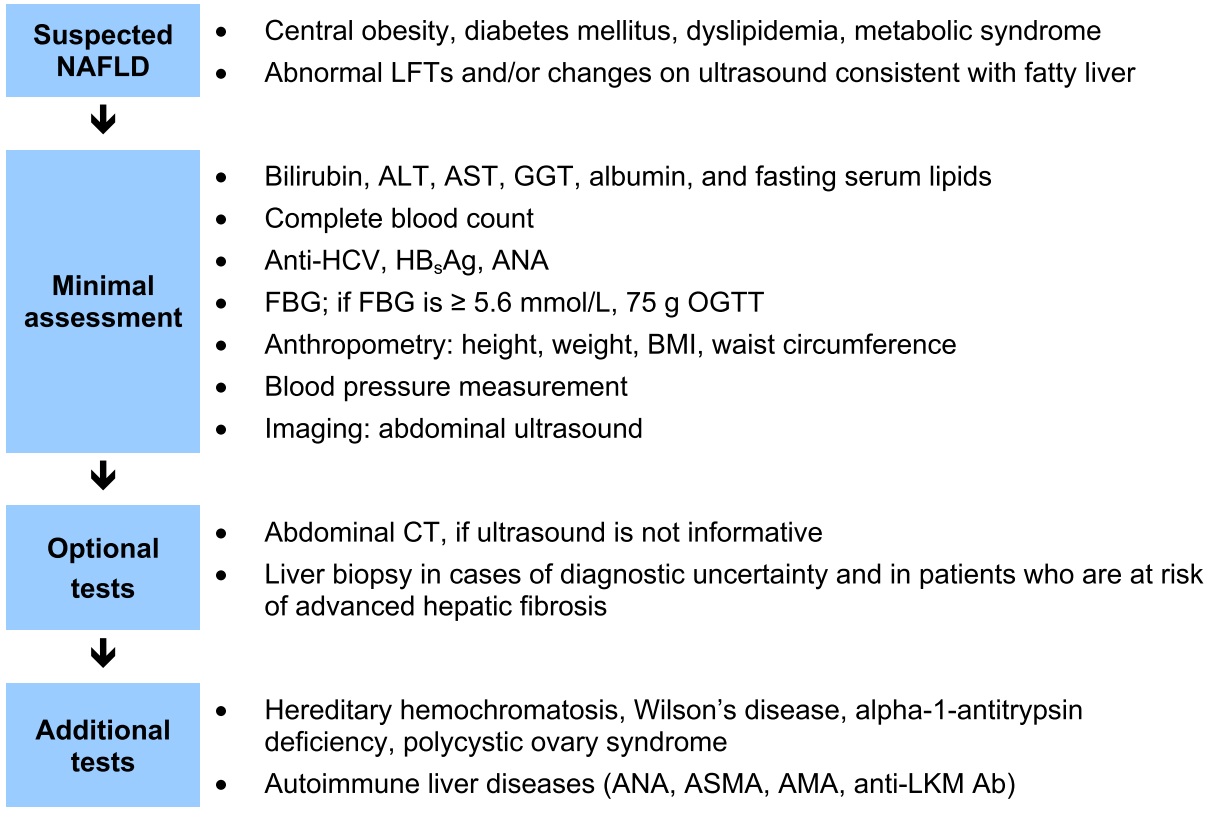

FIGURE 2. Diagnostic options for NAFLD. ALT indicates alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; anti-LKM Ab, anti-liver–kidney microsomal antibody; ASMA, antismooth muscle antibody; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; FBG, fasting blood glucose; GGT, γ-glutamyl transferase; HB_sAg, hepatitis B surface antigen; HCV, hepatitis C virus; LFT, liver function tests; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test. full color online

considered early, as most programs will decline such surgery for patients who are already cirrhotic. Limited studies have reported a dramatic improvement in liver disease, as well as other complications of metabolic syndrome/insulin resistance, following successful bariatric surgery.

- Drugs targeting insulin resistance, such as thiazolidinediones and metformin, are approved for diabetes therapy but not for NAFLD/NASH, and should be considered experimental (see the reference list below for more information and detailed discussion).

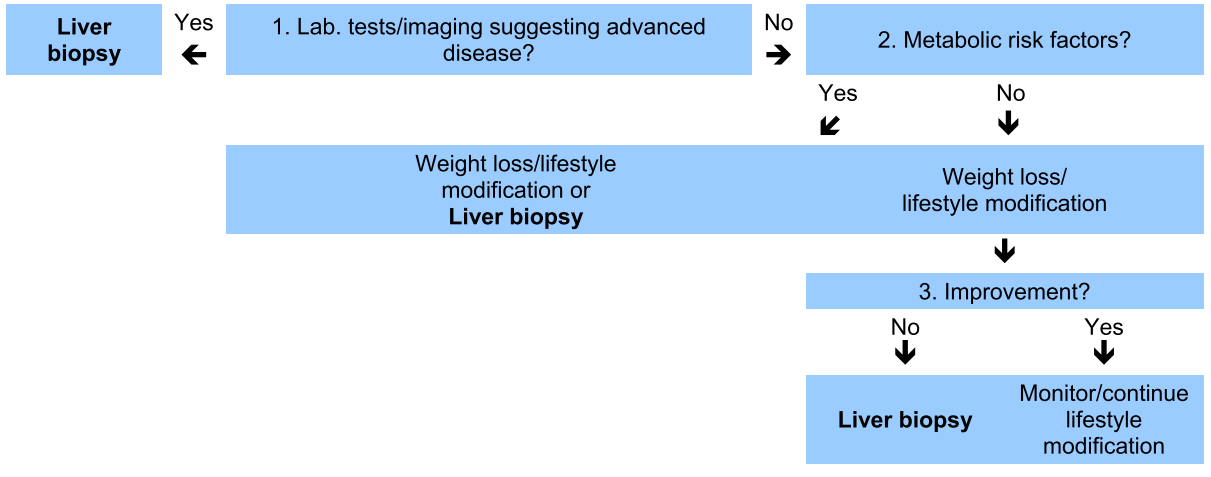

FIGURE 3. Algorithm for liver biopsy in patients with suspected nonalcoholic fatty liver disease after exclusion of other liver diseases. full color online

TABLE 2. Diagnostic Cascade for Extensive, Medium, and Limited Resources

	Availability	Feasibility	Remarks
Level 1—extensive resources			
1 Medical and family history to evaluate for risk factors; alcohol intake is a critical part of the patient history	Limited medical training required	Access to patients. Reliable history may be problematic	First step to identify potential patients: >20 g/d in females >30 g/d in males
2 General physical examination to evaluate for risk factors, BMI, and waist-hip ratio	Limited medical training required	Access to patients	
3 Test serum liver aminotransferases	Yes	Generally available	May be normal
4 Radiologic evaluation	Ultrasound; MRI more quantitative	Generally available	Insensitive if <33% fat; cannot distinguish alcoholic steatohepatitis from NASH
5 Serology to exclude viral hepatitis	HB_sAg, HCV Ab, HEV Ab when appropriate	Generally available	May coexist with NASH and exacerbate progression
6 Fasting blood sugar, lipid profile, HbA_{1c}	Readily available		
7 Screen for insulin resistance	Should be readily available		Would require further NAFLD/NASH evaluation if screen was positive
8 Rule out other chronic liver diseases	Optional and additional tests (see Fig. 2)	Generally available; expensive but important to rule out treatable coexistent diseases	Cost may be limiting
9 Liver biopsy and histology	Generally available	Requires experienced pathologist	The definitive test to rule out other diseases, grade and stage disease; cannot reliably distinguish NASH from alcoholic steatohepatitis
Level 2—medium resources			
1 Medical and family history and history of alcohol intake			
2 General physical examination to evaluate for risk factors, BMI, and waist-hip ratio			
3 Test serum liver aminotransferases			
4 Imaging evaluation: ultrasound			
5 Serology to exclude viral hepatitis: HB_sAg, HCV Ab, HEV Ab			
6 Fasting blood sugar, lipid profile, HbA_{1c}			
7 Screening for insulin resistance			
8 Rule out other chronic liver diseases: optional/additional laboratory tests (see Fig. 5; not all may be available)			
9 Liver biopsy and histology			
Level 3—low resources			
1 Medical and family history and history of alcohol intake			
2 General physical exam to evaluate for risk factors, BMI, and waist-hip ratio			
3 Test serum liver aminotransferases			
4 Radiologic evaluation: ultrasound			
5 Serology to exclude viral hepatitis: HB_sAg, HCV Ab, HEV Ab			
6 Fasting blood sugar, cholesterol, triglycerides			

Ab indicates antibody; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; HB_sAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Antioxidants and Antifibrotic Agents

Antioxidants and antifibrotic agents, such as vitamin E and pentoxifylline, have not been approved for NASH/NAFLD treatment. For all of them, there are limited data and few if any data from double-blind controlled trials. They are all considered experimental (see the reference list below for more information and detailed discussion).

Cascades: Options for Therapy

See Table 3.

SUMMARY

- NAFLD and NASH represent a major global public health problem, which is pandemic and affects rich and poor countries alike.
- There is insufficient evidence to justify screening for NASH/advanced liver disease in the general population.
- The diagnosis should be sought in all patients who present with risk factors for NASH. Not all patients with risk factors will have NAFLD or NASH, and not all patients with NASH will have standard risk factors.
- Not every person with fatty liver needs aggressive therapy.
- Diet and exercise should be instituted for all patients.
- Liver biopsy should be reserved for those patients who have risk factors for NASH and/or other liver diseases.
- Patients with NASH or risk factors for NASH should first be treated with diet and exercise. Vitamin E or pentoxifylline may be added in these patients. Experimental therapy should be considered only in appropriate hands and only in

TABLE 3. Therapy Cascades for Extensive, Medium, and Limited Resources

	Availability	Feasibility	Remarks
Level 1—extensive resources			
1 Weight loss diet (individually planned diet, based on measurements of total and resting energy expenditures), exercise, education	Well-trained health care providers available	Well-trained doctors, nurses, dietitians, exercise/ physiotherapy providers available	Lifestyle changes are the single most effective weapon in treating NASH; an enthusiastic support group is very helpful
2 Diabetes control	One of the key risk factors; well-recognized health problem	Physicians, nurses, dietitians readily available with appropriate training	Essential to control if present
3 Lipid-lowering agents	Readily available; dietary changes also essential	Physicians, nurses, dietitians readily available with appropriate training	Essential to control if present
4 Weight loss—bariatric surgery	Widely, although not universally available	Major surgery; still requires extensive lifestyle changes; likely not available if the patient is already cirrhotic or has portal hypertension	Should be considered early, before the patient has cirrhosis/portal hypertension; has been shown to reverse many of the problems of NASH/metabolic syndrome
5 Liver transplantation	Generally available in high-resource countries, but not in all centers or cities	Generally not available to patients with BMI >45 (>35 in some centers)	NASH may recur or develop de novo in the transplanted liver
Level 2—medium resources			
1 Weight loss diet (25% calorie restriction from recommended value), exercise, education	Limited training required for health care provider	Limited training required for health care provider	Lifestyle changes are the single most effective weapon in treating NASH; an enthusiastic support group is very helpful
2 Diabetes control	One of the key risk factors; well-recognized health problem	Physicians, nurses, dietitians more often available with appropriate training	Essential to control if present
3 Lipid-lowering agents	May be less available due to cost; dietary changes will also help if hyperlipidemia is present	Physicians, nurses, dietitians more often available with appropriate training	Important to control if present
Level 3—limited resources			
1 Weight loss diet, exercise, education	Limited training required for health care provider	Limited training required for health care provider	Lifestyle changes are the single most effective weapon in treating NASH; an enthusiastic support group is very helpful
2 Diabetes control	One of the key risk factors; well-recognized health problem	Generally available	Essential to control if present
3 Lipid-lowering agents	Becoming more widely available with good and cheaper generics; dietary changes will also help if hyperlipidemia is present	Require resources for medications, training of health care providers	Important to control if present

NASH indicates nonalcoholic steatohepatitis.

patients who fail to achieve a 5% to 10% weight reduction over 6 months to 1 year of successful lifestyle changes.

- Bariatric surgery should be considered in patients in whom the above approaches fail, and it should be performed before the patient becomes cirrhotic.
- Liver transplantation is successful in patients who meet the criteria for liver failure; however, NASH may recur after transplantation and is likely to be denied to patients with morbid obesity.
- NAFLD and NASH are also becoming an increasingly serious problem in pediatric patients, including those under the age of 10.
- Ultimately, NAFLD and NASH are diagnoses of exclusion and require careful consideration of other diagnoses. Just as the clinician cannot diagnose NASH on the basis of clinical data alone, the pathologist can document the histologic lesions of steatohepatitis, but cannot reliably distinguish those of nonalcoholic origin from those of alcoholic origin.

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Position statements and reviews:

Insufficient randomized, controlled, double blind studies are available to provide evidence-based data for a formal guideline, as discussed in the Introduction above. The following is a listing of selected position statements, reviews, and expert opinion articles.

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For those wishing additional information and documentation of the basis for the recommendations given in this guideline, further references are available in the expanded online version of it, listed under the headings of epidemiology, pediatric epidemiology, histologic diagnosis, noninvasive diagnosis, hepatitis C and NAFLD/NASH, pathophysiology, and treatment.