Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal serum aminotransferase levels in both developed and developing countries. Globally, the prevalence of NAFLD is rising as a result of increasingly sedentary lifestyle, globalization of Western diet, and improving food supplies in famine-stricken areas of the past. Although data are limited regarding the incidence trends of NAFLD, it would not be unexpected that rising incidence is observed because of the trends in obesity and obesity-related diseases. However, both incidence and prevalence trends must be interpreted with caution, because improved understanding, awareness, and diagnosis of NAFLD may also be influenced by misclassification biases and selection biases. Furthermore, the prevalence estimates of NAFLD can vary depending on the population studied and the accuracy of the diagnostic test. Despite these limitations, it is currently estimated that the global prevalence of NAFLD is as high as 1 billion. In the United States, NAFLD is estimated to be the most common cause of chronic liver disease, affecting between 80 and 100 million individuals, among whom nearly 25% have NASH. This form of NAFLD is characterized by histologic evidence of progressive hepatocellular injury (ballooning and inflammation) that can lead to cirrhosis and cirrhosis-related complications such as hepatocellular carcinoma (HCC) and need for liver transplantation (LT). Although previous studies have demonstrated the increasing rates of NASH-related LT from 1.2% in 2001 to 9.7% in 2009 to become the third most common indication for LT in the United States, a recent study using registry data from the United Network for Organ Sharing/Organ Procurement Transplant Network demonstrated that in 2013, NASH became the second leading etiology of liver disease among adults awaiting LT in the United States and is predicted to become the leading indication for LT in the near future. In addition, NASH is currently the...
second leading etiology and the most rapidly growing indication among adults with HCC undergoing LT in the United States.

**Nonalcoholic Fatty Liver Disease: Natural History and Predictors of Outcome**

The risk of NASH progressing to cirrhosis has not been clearly delineated, but it has been estimated to range from 21% to 26% during 8.2 years. Up to 30% of NASH patients with compensated cirrhosis develop hepatic decompensation in 8–10 years. Although the development of cirrhosis among NAFLD patients increases the risk of developing cirrhosis-related complications such as HCC and hepatic decompensation, earlier stages of fibrosis can also predict worse outcomes. Fibrosis stage is the strongest predictor for aggressive natural history of illness. Individuals with a tendency for binge drinking have a higher risk for alcoholic steatohepatitis. Fortunately, most patients with NASH will outlive their liver disease and are more likely to develop fatal complications from cardiovascular disease. Therefore, the protective role of modest alcohol use to reduce morbidity and mortality associated with underlying cardiovascular disease needs further evaluation.

Meta-analysis suggests that modest alcohol use may favorably impact the prevalence of NAFLD and progression to NASH. However, these data must be reproduced in a prospective fashion and remain controversial. On the contrary, large prospective cohort studies have demonstrated that obesity and alcohol use can multiply the risk of liver-related death and HCC.

NAFLD is referred to as the hepatic manifestation of metabolic syndrome. Typically, most cases of metabolic syndrome–related NASH present with characteristic features of metabolic syndrome: central obesity, impaired glucose tolerance, high triglycerides, and low high-density lipoprotein (HDL). In addition to high triglycerides and low HDL, patients with NAFLD are also noted to have higher low-density lipoprotein (LDL) particle concentration and lower LDL particle size. The abnormalities in lipoprotein profile in patients with NAFLD are suggestive of deranged lipid metabolism. Whereas concurrent features of metabolic syndrome increase the risk of developing NAFLD, the presence of NAFLD also increases the risk of developing complications such as dyslipidemia and insulin resistance. The high prevalence of metabolic syndrome features observed among NAFLD patients emphasizes the importance for evaluating for these risk factors so that early intervention can be implemented to improve long-term outcomes.

**Nonalcoholic Fatty Liver Disease: Diagnosis**

The diagnosis of NAFLD incorporates the clinical history, laboratory data, radiographic data, as well as histologic information. NAFLD can be diagnosed non-invasively by the finding of hepatic steatosis on abdominal imaging study; liver biopsy is not always needed to confirm the diagnosis. However, a liver biopsy is required to distinguish isolated steatosis from NASH and to stage fibrosis severity, which may subsequently affect risk of disease progression and disease management.

Three key histologic features are needed to confirm the diagnosis of NASH and include steatosis, inflammation, and cellular ballooning.

**Diagnosis: Abdominal Imaging**

An abdomen ultrasound is operator dependent and lacks sensitivity in NAFLD patients with less than 30% steatosis on liver biopsy. However, ultrasound is noninvasive, without contrast-related risks, preferred by patients, and widely available. Computed tomography is a radiation hazard, introduces contrast-related risks, has low sensitivity for hepatic fat mapping, and is expensive. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) provide the highest precision (sensitivity and specificity) in quantifying steatosis and liver fat mapping. On the basis of promising emerging data, MRI and MRS may become the gold standard for the diagnosis and management of NAFLD in the near future, although they are currently limited by cost and availability. Currently, abdominal imaging studies are unable to accurately diagnose NASH. The role of transient elastography may be limited in subjects with high body mass indices. In patients with NAFLD, a hepatic stiffness measurement with magnetic resonance elastography (MRE) is superior to MRI for the noninvasive diagnosis of significant liver fibrosis and cirrhosis. In addition, MRE may help identify individuals with steatohepatitis even before the onset of significant fibrosis, although further studies are needed to validate this finding. NAFLD with inflammation but without fibrosis demonstrates greater hepatic stiffness.
than isolated steatosis and lower mean stiffness than NAFLD with fibrosis.31

**Diagnosis: Liver Biopsy**

Diagnosis of NASH requires a liver biopsy to confirm the characteristic histologic features. The considerable disease burden of NASH in the United States and the invasive nature of a liver biopsy have prompted experts to consider its selective use in NAFLD patients with higher likelihood of progression to NASH. An individualized assessment is needed with discussion of risks and benefits of a diagnostic liver biopsy. Early diagnosis of NASH has crucial management implications, and these patients may benefit from off-label therapy with promising agents (vitamin E and pioglitazone) or treatment in the setting of a therapeutic clinical trial.32–37 In the setting of advanced fibrosis or cirrhosis, steatosis may be absent.33,32 Interobserver variability and diagnostic interpretation can vary across experienced pathologists.23,24,38,39 The lack of agreement between pathologists regarding hepatocellular ballooning or sampling error may have resulted in a lower number of patients meeting the entry criteria in clinical trials.32 Therefore, a liver biopsy has several limitations as a diagnostic modality in patients with NASH. Patients who are noted to have isolated hepatic steatosis with any degree of necroinflammation on an index liver biopsy are at increased risk for progressive histologic damage, albeit at a lower rate than those with NASH.33,41 In addition, patients with isolated hepatic steatosis and inflammation on liver biopsy and with clinical diagnosis of metabolic syndrome or individual components of metabolic syndrome may be at risk for more rapidly progressive histologic damage.40,41

**Table 1.** Predictors of Histologic Evidence of NASH on Index Liver Biopsy

| Body mass index greater than 30 kg/m² |
| Persistently abnormal liver enzymes with AST greater than ALT |
| Metabolic syndrome with elevated AST and ALT |
| Diabetes mellitus (type 2) with elevated AST and ALT |
| Hypertension |
| High triglycerides and low HDL |
| Family history of diabetes mellitus |

AST, aspartate aminotransferase.

**Nonalcoholic Fatty Liver Disease: Treatment and Outcomes**

Many controversies have persisted with respect to treatment of NAFLD.1 Chief among these is the inherent limitations in our ability to accurately distinguish different stages of NAFLD, because targeted therapy for
NAFLD requires precise categorization of NAFLD into nonalcoholic fatty liver or NASH. A proactive treatment approach is prudent in patients with biopsy-proven NASH because of the risk of progressive histologic damage. Several promising pharmacologic agents need to be further studied in patients with NASH. The most fundamental step in the management of NAFLD is treating the risk factors that are commonly associated with metabolic syndrome through lifestyle modifications, which may serve as both primary and secondary prevention for NAFLD.

Treatment and Outcomes: Exercise Program

The adverse consequences of obesity, diabetes mellitus, and other components of metabolic syndrome in patients with NAFLD are further compounded by the lower level of physical activity and lack of aerobic exercise noted in this patient population. It appears that exercise alone, independent of weight loss, may result in histologic improvement in these patients. It is suggested that 120 minutes of aerobic exercises such as running and swimming every week increase glucose uptake by improving insulin sensitivity. Exercise stimulates protein synthesis and improves muscle mass, whereas sedentary lifestyle leads to muscle breakdown. Incremental rise in fat-free, lean mass induced by aerobic exercise results in efficient glucose uptake with reduction in hepatic fat content and provides protection against NAFLD. A systematic review that analyzed data from randomized controlled trials noted that exercise can reduce hepatic fat content without affecting ALT. An individualized exercise regimen needs to be developed that is based on the severity of underlying hepatic dysfunction from NAFLD, class of obesity, exercise tolerance status, presence of individual components of metabolic syndrome, and other comorbid medical problems in a given individual.

Treatment and Outcomes: Dietary Modifications

It is important to establish a detailed dietary plan to effectively manage the daily caloric intake in conjunction with exercise to induce weight loss without malnutrition. On the basis of observations from small studies, a weight loss of 7% or more with intense dietary counseling during 1 year may improve histology in patients with biopsy-proven NASH. Most guidelines regarding hypocaloric diet suggest 1000–1200 calories per day for women and 1200–1600 calories per day for men with a goal to achieve a weight loss of 0.5–1.0 kg per week. Macronutrients including carbohydrate, protein, and fat and micronutrients including vitamins, minerals, and supplements must be balanced. It has been demonstrated that more durable weight loss can be achieved in patients with NAFLD by combining diet and exercise for longer than 12 months. Data on the role of certain nutritional supplements to improve exercise performance are encouraging. Caffeine improves performance and may be protective against the development of NAFLD. Data from the National Health and Nutrition Examination Survey showed that 2 cups of caffeinated coffee per day associated with a lower risk for NAFLD, suggesting a potential protective effect. Consumption of caffeinated coffee is associated with a significant risk reduction of fibrosis in the setting of NASH.

Treatment and Outcomes: Pharmacotherapy

In addition to weight reduction strategies to address obesity-related NAFLD, a number of medical therapies have been studied in patients with NASH. These include antioxidants such as vitamin E, insulin sensitizers such as pioglitazone and metformin, lipid-lowering agents such as statins, and cytoprotective agents such as ursoodeoxycholic acid. Despite decades of clinical trials, current evidence suggests that only vitamin E may be beneficial for treatment of nondiabetic patients with NASH, but no single treatment can be recommended to all patients with NASH. Thiazolidinediones are selective peroxisome proliferator–activated receptor-gamma agonists with clinical evidence of therapeutic benefit. Thiazolidinediones improve insulin sensitivity of adipose tissue, liver, and muscle. Pioglitazone demonstrated hepatic histologic benefit in clinical trials by improving steatosis, lobular inflammation, and ballooning degeneration. Subsequently in a clinical trial, 247 nondiabetics with histologic evidence of NASH were randomized to 1 of 3 groups to receive pioglitazone 30 mg, vitamin E 800 IU, or placebo for 96 weeks. The primary end point was evaluated by NAFLD Activity Score and required histologic improvement in NASH including hepatocyte ballooning. Although the primary end point was not met in the pioglitazone group, faulty randomization of balloon degeneration in the pioglitazone group compared with the other 2 groups may have limited the study’s ability to detect a significant benefit. It is important to recognize that 47% of the subjects receiving pioglitazone demonstrated complete resolution of steatohepatitis at end-of-treatment biopsy versus 21% in the placebo group (P = .001). In summary, the clinical trial provided evidence that optimization of insulin sensitivity is pivotal in the management of NASH. Two meta-analyses of randomized controlled trials showed that pioglitazone was able to promote regression of hepatic fibrosis in patients with NASH. In addition, pioglitazone may reduce mortality related to ischemic cardiovascular events, which is the most common cause of death in patients with NASH. However, pioglitazone has a Food and Drug Administration black box warning in the United States that it may precipitate congestive heart failure in at-risk individuals, without any increase in cardiovascular or all-cause mortality. Overall, pioglitazone has a favorable safety profile and is
logic damage. The improvement in NASH-related liver histology among NAFLD patients with or without diabetes.

Vitamin E supplementation with 800 IU/day that was studied in a large, double-blind, randomized, placebo-controlled trial demonstrated superiority versus placebo by improving ALT levels and NASH-related histologic damage. The improvement in NASH-related inflammation and fibrosis noted with vitamin E therapy was most likely induced by suppression of lipid peroxidation and oxidative stress.

In a meta-analysis, vitamin E supplementation increased all-cause mortality, possibly related to unfavorable changes in plasma lipoproteins. Although these data have been challenged, it is important to keep in mind that therapy with high-dose vitamin E may not be without adverse effects. The available evidence suggests that vitamin E improves liver enzymes, steatosis, and liver injury in NASH patients without diabetes. There are insufficient data to recommend vitamin E for patients with NASH and concomitant diabetes or cirrhosis. Importantly, there are no prospective data demonstrating that pioglitazone or vitamin E improves fibrosis, which may be the most relevant histologic end point.

Bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid) is a potent activator of the farnesoid X nuclear receptor that reduces liver fat and fibrosis in animal models of fatty liver disease. Obeticholic acid improved the histologic features of NASH, but its long-term benefits and safety need further clarification.

A recently published study by the NASH clinical research network, the FLINT trial, reported findings of a multi-center, double-blind, placebo-controlled randomized clinical trial evaluating the effect of obeticholic acid treatment among non-cirrhotic patients with NASH. Among patients treated with obeticholic acid, 45% achieved improved liver histology (defined as a decrease in NAFLD activity score by at least 2 points without worsening of fibrosis from baseline to the end of treatment) compared with 21% among the placebo group (relative risk, 1.9; 95% confidence interval, 1.3–2.8). Although more studies are needed to confirm the potential beneficial effect of obeticholic acid, the FLINT trial provides promising outcomes.

Another potential therapy in phase 2 clinical trials is simtuzumab, an antifibrotic monoclonal antibody that targets the lysyl oxidase-like 2 (LOXL2) enzyme. Data from these trials in both stage 3 and 4 NASH patients are eagerly anticipated. Pentoxifylline is another agent that has shown promise in smaller pilot trials. It appears that these beneficial effects are at least partly mediated through decreasing oxidative stress. However, future studies in larger groups of patients are needed to substantiate these results.

### Treatment and Outcomes: Surgical Options

Despite the high prevalence of NAFL and NASH among morbidly obese surgical patients, this condition was not associated with increased risk for postoperative complications after bariatric surgery. In the setting of cirrhosis, bariatric surgery is only indicated in patients with compensated cirrhosis and contraindicated for patients with hepatic decompensation.

Bariatric surgery is associated with the most rapid, sizable, and durable weight loss and ranges from 20% to 40%. Approximately 75% of weight loss is sustained for at least a decade or longer after bariatric surgery. The most commonly used laparoscopic bariatric surgeries include Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and adjustable gastric band. The routine use of laparoscopic approach has resulted in lower postoperative complication rates related to surgical wound and perioperative mortality. It is recommended that patients be monitored for deficiencies in iron, vitamin B12, calcium, and vitamin D.

Because of the profound weight loss associated with bariatric procedures, the impact on outcomes is significant. Patients with nonalcoholic fatty liver and NASH demonstrate histologic improvement with reduction in mortality from NASH-related complications after bariatric surgery. An impressive reduction in all-cause mortality of 30%–40% has been reported within the 7–10 years after the bariatric procedure, with the largest improvement in survival from diabetes, cardiovascular disease, and obesity-related malignancies.

LT can be pursued in patients with hepatic decompensation in the setting of cirrhosis. Combined LT plus sleeve gastrectomy for obese patients who failed to lose weight before LT have been reported. In a single center study with small sample size of patients undergoing the combined LT and sleeve gastrectomy, there were no deaths or graft losses, none of the patients developed diabetes or steatosis after LT, and all showed significant weight loss. These data were limited by a small sample size and lack of long-term follow up.

### Conclusion

With the rising rates of obesity and obesity-related diseases, the worldwide prevalence of NAFLD has also demonstrated similar trends. Although the importance of awareness can lead to early diagnosis of NAFLD, few pharmacologic treatment options are currently available. Clearly, lifestyle and dietary programs can provide
significant benefit; these strategies are not successful in all and may not prove effective in patients with advanced stage or decompensated disease. Although there is evidence supporting a beneficial effect of some pharmacologic agents, to date, there is no formally approved medical therapy for NASH, and the magnitude of these improvements is small. Ongoing and future trials will hopefully offer additional and more effective therapies for the growing number of patients with chronic liver disease caused by NASH. A major limitation of the current data is that only a fraction of patients respond to therapy, and no agent has been convincingly shown to decrease fibrosis, arguably the most relevant therapeutic end point. Furthermore, trials exploring the potential additive effects of insulin sensitizers with cytoprotective agents or other modalities are eagerly awaited. As a result, there is a major unmet need for therapeutic options for the growing number of patients with NASH-associated cirrhosis. Management of NASH (Figure 1), like that of other complex metabolic diseases, will necessitate a multidisciplinary approach.

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Reprint requests
Address requests for reprints to: Stephen A. Harrison, MD, Division of Gastroenterology, San Antonio Military Medical Center, Fort Sam Houston, Texas 78234. e-mail: Stephen.a.harrison.mil@mail.mil; fax: (210) 916-2601.

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Conflicts of interest
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1. Which histologic feature(s) of NAFLD is best at predicting disease-specific mortality:
   a. ballooning
   b. amount of fat
   c. fibrosis
   d. Mallory bodies
   e. inflammation

   **True or False**

2. To be effective in improving histology in NAFLD, exercise must be accompanied by weight loss

3. NAFLD is defined as >5% fat in the liver, ultrasound becomes reliably abnormal only when fat is present in >30% of hepatocytes

4. Exclusion of alcohol intake to diagnose NAFLD requires a history of <3 drinks (<30 grams) a day for men and <2 drinks a day for females

5. Neither vitamin E nor pioglitazone therapy have been shown to improve NAFLD-related fibrosis

6. Weight loss goal that has been found to improve NAFLD is about 5% to 10% weight loss.

7. During 8-10 years of follow up, NASH progresses to cirrhosis in about 75% of patients

8. Metformin therapy results in significant histologic improvement in patients with NAFLD

9. All three feature - steatosis, inflammation and ballooning must be present to diagnose NASH histologically

10. Vitamin E therapy efficacy in NAFLD has been shown in non-diabetic patients

11. The presence of NASH is associated with increased morbidity and mortality for patients undergoing gastric bypass