Non-alcoholic Steatohepatitis (NASH): Prevalence, Diagnosis, Management, and Emerging Therapies

TARGET AUDIENCE

- Lipidologists
- Endocrinologists
- Cardiologists

PROBLEM STATEMENT

Non-alcoholic fatty liver disease (NAFLD) affects up to 25% of people in the United States and is the leading cause of chronic liver disease in the Western World.[1-3] Non-alcoholic steatohepatitis (NASH) is the most aggressive subtype of the disease during which the accumulation of liver fat is accompanied by cellular injury and inflammation.[4] The disease can progress to fibrosis, cirrhosis, and/or hepatocellular carcinoma (HCC).[1-4] In fact, HCC caused by NASH is now the second leading cause of liver transplants in the United States and is poised to become the leading cause of transplants by 2020.[1,5]

It is estimated that NASH affects 2-5% of Americans.[6] However, the actual prevalence of NASH may be considerably higher due to the challenge of identifying patients with the disease. Several studies have reported that clinicians are unaware of the prevalence of NASH.[6] Perhaps as a result, NAFLD patients frequently remain undiagnosed until the disease progresses and complications, such as cirrhosis and HCC, arise.[7] This is troubling since the overall and liver-related mortality in patients with cirrhosis is high for NAFLD, approaching 80% and 55% respectively after 12 years.[7-9] Furthermore, new evidence suggests that many clinicians may be overlooking clinical, radiologic, or laboratory evidence of advanced disease already in the medical charts of NAFLD patients that remain undiagnosed with NASH.[7] Approximately three quarters of undiagnosed patients in this same study had diabetes and were at high risk for NAFLD and NASH.[7] Improved clinician education about NASH, its prevalence, and its associated risk factors could help improve screening and diagnosis of the disease.

Additionally, many clinicians may not be aware of the best practices for managing the disease. A recent study indicated that clinician management of the disease often deviates significantly from published practice guidelines and/or available position statements.[6,10] This may lead clinicians to underutilize evidence-backed treatment regimens, ineffectively monitor the progression of the disease, or fail to recommend patients to specialists at the appropriate time.[6,10] The American Association for the Study of Liver Diseases in concert with the American College of Gastroenterology and the American Gastroenterological Association released the most widely used guidelines in 2012.[11] It is critical that physicians stay apprised of these guidelines along with the latest recommendations and position statements in order to best serve NAFLD and NASH patients.

Although published guidelines can provide an essential knowledgebase for clinicians, there remains a definite deficiency in management strategies for NASH. Although effective, sustained weight loss through lifestyle modification can be difficult to achieve and sustain for many patients.[1,12] Unfortunately, there are also currently no pharmacotherapies approved by the Food and Drug Administration (FDA) specifically tailored to the disease.[1,12] Published guidelines recommend the off-label use of drugs like pioglitazone, vitamin E, and statins, but only in certain patient populations.[11,12]

Interestingly, developments in our understanding of the pathogenesis of the disease in recent years have led to some promising new investigational drugs. Improved clinician understanding of NASH pathogenesis could be critical to navigating the numerous emerging treatments for NAFLD and NASH that range widely in their metabolic targets.[1,12,13] Emerging treatments that target metabolic pathways involved in fat accumulation and resultant metabolic stress include PPAR agonists (eg, elafibranor, saroglitazar), FXR agonists (eg, AKN-083, obeticholic acid), inhibitors of de novo lipogenesis (eg, aramchol, NDI010976), GLP-1 agonists (eg, liraglutide, exenatide), and FGF analogs (eg, NGM-282). [1, 12-14] Meanwhile, emerging treatments that target metabolic pathways involved in inflammation, cell injury, and oxidative stress also show promise and include immune modulators (eg, cenicriviroc, amlexanox), medications that target the TNFα pathway (eg, pentoxifylline), and antioxidants like vitamin E.[1,12,13] Investigational medications that target metabolic processes in the gut are also promising and include anti-obesity agents (eg, orlistat) along with treatments that modulate the gut microbiome (eg, solithromycin, IMM-124e).[1,12,13] Medications that target metabolic pathways involved in fibrosis are also currently in the clinical pipeline, including antifibrotic agents (eg, simtuzumab) along with some medications that have multiple targets or targets involved in different aspects of disease progression (eg, cenicriviroc, elafibranor).[1,12,13] Finally, preliminary efforts to identify effective combination therapies (eg, cenicriviroc with evogliptin, GS-4997 with simtuzumab) are also already underway.[15,16]

Outside of emerging pharmacotherapies, several endoscopic interventions and recently approved surgical approaches could assist patients continuing to struggle with weight loss.[13,17] Educating clinicians about all new advances could help them navigate the rapidly changing treatment landscape to better serve patients and improve overall morbidity and mortality for NAFLD and NASH.

STATEMENT OF NEEDS

Clinical Practice Gap #1: Identifying NAFLD patients with NASH can be challenging. Clinicians that treat NAFLD patients under recognize NASH despite its high prevalence.[6] The disease frequently progresses silently and can go unnoticed until it has already reached advanced stages like cirrhosis and HCC.[1] Clinicians who treat cardiometabolic diseases should have a heightened awareness of the NASH and the NAFLD populations that are at greatest risk for the disease.

Educational Need #1: Clinicians that treat cardiometabolic disease should recognize the prevalence of NASH in NAFLD patients. The increasing rates of obesity and diabetes across the United States are causing more clinicians to encounter patients with diagnosed and undiagnosed NAFLD and NASH.[10] Despite this, clinicians often underestimate and misunderstand the disease. One study in Wisconsin found that 84% of clinicians surveyed underestimated the rate of NAFLD in the population.[18] A more recent study further supported this by finding that one-third of providers underestimated the rate of occurrence of NAFLD by over 15-20%.[10] Another investigation highlighted that more than half of surveyed primary care physicians remained unaware of the differences between NASH and NAFLD, despite that 58% of these physicians treated patients for cardiometabolic diseases.[6] This may contribute to the ability of NASH to remain undiagnosed until more advanced stages of the disease. A recent study of patients with NAFLD cirrhosis awaiting live transplants were not diagnosed with NAFLD until they presented with complications of portal hypertension.[19] Even more troubling was that 60% of these patients had diabetes, one of the highest risk factors for the NAFLD and NASH.[19] It is

important to increase clinician awareness of risk factors so that patients with a high likelihood of NASH histology can be monitored more closely or even referred to specialists.[7,19] Patients with diabetes, older age, a high BMI, or even those that have a relative already diagnosed with fatty liver disease are at higher risk.[5,20] Additionally, patients that work late shifts or have other living conditions that cause them to eat late-night meals could also be at higher risk since it may upset the circadian rhythm of hepatic metabolic pathways.[21] Clinician awareness of the risks associated with these patient populations could lead to earlier detection and treatment of NAFLD and NASH.

Educational Need #2: Many clinicians are not aware of screening guidelines and fail to take appropriate diagnostic approaches with patients. The practice guidelines released in 2012 recommend liver biopsies as the gold standard for diagnosing patients.[11] However, biopsies are impractical and cost prohibitive, leading many clinicians to use noninvasive methods, like aminotransferase serum levels, ultrasounds or computed tomography scans.[6,10,22] Unfortunately, there is still no consensus on specific biomarkers that could be used in alternative screening methods, and other noninvasive methods are simply not as effective or as accurate as a liver bioposy.[6,22]

Despite this, clinicians continue to utilize noninvasive methods, often without confirming their diagnosis with a liver biopsy. One study found that clinicians overly relied on aminotransferase levels to screen patients for NAFLD and NASH despite the well-recognized fact that levels are a poor marker for disease progression and can remain normal in cases of the disease.[10] Non specialist clinicians in particular may be unaware of the screening and diagnostic guidelines for NAFLD and NASH. One study surveying the awareness and practices in over 300 clinicians found that 75% of surveyed PCPs diagnosed patients with NASH without the use of a liver biopsy.[6] Even some specialists may not be aware of guidelines. The same study found that 63% of patients under the care of a specialist that had been diagnosed with NASH using a noninvasive technique were not recommended a liver biopsy to confirm the diagnosis.[6]

Improved awareness of screening guidelines could help clinicians diagnose NAFLD and NASH earlier and more effectively. Currently, clinicians often do not diagnose patients until the disease has advanced to evidence of cirrhosis and/or HCC.[7,19,] One study examining 100 patients with NAFLD cirrhosis found that the majority of patients (66%) were not intentionally diagnosed with the disease by clinicians but were instead diagnosed incidentally due to complications or tests performed for reasons unrelated to liver disease.[7]

Clinical Practice Gap #2: Clinician management of the disease frequently diverges from published practice guidelines.[6] This may lead clinicians to ineffectively monitor the progression of the disease, underutilize data-backed therapies, or fail to recommend patients to specialists for monitoring and treatment.[6,10]

Education Need #3: Clinicians need to be up-to-date on published management guidelines for the disease to ensure that patients receive the most appropriate evidence-backed therapies. Data-backed therapies like lifestyle changes to promote sustained weight-loss in patients and off-label use of medications like pioglitazone, vitamin E, and statin medications have been shown to be effective and are recommended for the treatment of some patient populations.[11] However, these treatments may also carry some risks and are not recommended for all patients.[11] For example, treatment with vitamin E is associated with an increased risk of

hemorrhagic stroke and it has not been studied in patients with diabetes or cirrhosis.[11] Similarly, the long-term safety and efficacy of pioglitazone in NASH is not established and the drug has not been tested in diabetic populations.[11] Published guidelines therefore recommend that both drugs are only prescribed in some patient populations after confirmation of NASH with a liver biopsy.[11] Despite these clear guidelines, a recent investigation examining the practices of a population of gastroenterologists and hepatologists found that a quarter of clinicians prescribed pioglitazone or vitamin E without confirming NASH with a liver biopsy.[23]

Many clinicians also continue to prescribe outdated treatments not backed by clinical evidence. One investigation surveying a range of clinicians found that 10% of specialists in the study reported treating patients with drugs not recommended by current guidelines.[6] Supporting this finding, another recent investigation found that 50% of clinicians prescribed metformin for patients diagnosed with NASH despite the lack of data supporting its use and the 2012 guidelines explicitly stating that it is not recommended for treatment of the disease.[6,11,24] Keeping clinicians up-to-date with the current published guidelines and position statements can help ensure that patients receive the most appropriate and safest evidence-backed treatment for their unique situation. Prescribing treatments backed by clinical evidence over outdated treatments could also improve patient outcomes.

Clinical Practice Gap #3: There is a current lack in effective management strategies for NAFLD and NASH. Treatments like lifestyle changes and off-label use of drugs described in published guidelines are better than outdated treatment regimens not backed by clinical data.[11] However, there is still significant room for improvement in management strategies for NAFLD and NASH patients. Sustained weight loss through lifestyle modification can be difficult to achieve and sustain for many patients.[1,12,15] There are also still no pharmacotherapies approved by the FDA specifically tailored to the disease.[1,12]

An increased understanding over the last several years of the pathogenesis of NAFLD and NASH has led to the development of a variety of promising new pharmacotherapies currently in clinical trials.[1,12,25] These emerging pharmacotherapies and some newly approved surgical therapies are poised to dramatically alter the treatment landscape of NAFLD and NASH.

Education Need #4: Clinicians need to be aware of the disease pathogenesis of NAFLD and NASH to better understand and select treatments from upcoming pharmacotherapies. The disease is traditionally thought to develop and progress in two waves. The "first hit" of the disease involves excessive accumulation of fat in the liver and results in metabolic stress.[26-29] Conversely, the, the "second hit" in the progression of the disease is characterized by signs like oxidative stress, inflammation, and cellular injury.[26-29] Continued cellular injury and disease progression can eventually lead to fibrosis and sometimes to cirrhosis and/or HCC.[1,12] Research advances over the past decade have improved our understanding of the variety of metabolic pathways involved in these stages and have help identify a large number receptors, enzymes, and other molecules that can serve as effective drug targets.[1,12]

Despite these recent advances, many clinicians may be unaware of even basic pathogenesis of the disease. Nearly half of surveyed PCP respondents in a study examining the practices of over 300 clinicians did not understand general differences between NAFLD and NASH and how the disease progressed.[6] Improved understanding of pathogenesis could help clinicians navigate

emerging treatments to select regimens with targets appropriate to the current stage of the patient's disease.

Understanding disease pathogenesis will become even more important as combination therapies become available.[12,16] Current understanding of NASH pathogenesis supports the idea that simultaneously targeting multiple pathways involved in the disease with different drugs could help boost the impact of treatments.[12] Clinician education of NAFLD and NASH pathogenesis could better equip clinicians to understand and select from emerging single and combinational treatments.

Education Need #5: Clinicians need to be aware of the many new and emerging treatment strategies to help navigate the rapidly changing treatment landscape of NADFL and NASH. As previously mentioned, there are a large number of new investigational pharmacotherapies that target different metabolic processes in the disease. However, one recent study examining PCPs and specialists found that 61% of PCPs and 36% of specialists were not aware of drugs currently in development.[6] This highlights the need to increase patient education about the wealth of new NAFLD and NASH treatments poised to soon become available.

Medications like PPAR agonists (eg, elafibranor, saroglitazar), FXR agonists (eg, AKN-083, obeticholic acid), inhibitors of de novo lipogenesis (eg, aramchol, NDI010976), GLP-1 agonists (eg, liraglutide, exenatide), and FGF analogues (eg, NGM-282) target various metabolic components involved in the excessive fat accumulation and metabolic stress characterized by the "first hit" of the disease.[26-28] For example, the PPARα/δ agonist elafibranor showed promise in NASH patients without cirrhosis in the phase 2b GOLDEN-505 trial[30] while the PPARα/γ agonist saroglitazar showed initial success against diabetic dyslipidemia.[31] Several other PPAR agonists holding considerable promise are also in the clinical pipeline.[1,12] Emerging drugs acting as FXR-agonsits could help improve prognosis in NAFLD patients, including AKN-083 which has shown high affinity, potency, and selectivity along with good tolerability in pre-clinical trials and is set to begin clinical trials in early 2017 .[14,32] Obeticholic acid, another FXR agonist further along in the clinical pipeline, showed significant histological improvement in patients participating in the FLINT trial, although there was some reversible worsening of the lipid profile in subjects.[33] Inhibitors of de novo lipogenesis, like aramchol which is currently in a phase 2b clinical trial, also represent a promising class of drugs in the treatment of NASH patients.[34] GLP-1 agonists like liraglutide or exenatide are already used for diabetes and new studies with NASH patients suggest they may help lower liver fat content, improve fibrosis, and decrease aminotransferase serum levels.[1,12] Finally, FGF analogues, like the FGF-19 analogue NGM-282 currently in a phase 2 clinical trial in NASH patients, could help suppress gluconeogenesis without any cancer-promoting effect on hepatocytes.[1,12,35]

Several emerging drugs that impact the later "second hit" stage of disease progression[28] also have considerable promise, including immune modulators (eg, cenicriviroc, amlexanox), medications that target the TNFα pathway (eg, pentoxifylline), and antioxidants like previously discussed use of vitamin E. A variety of investigational immune modulators show promise against NASH. For example, the dual CCR2/CCR5 pathway inhibitor cenicriviroc showed improvement in serum markers of fibrosis in HIV-infected patients[36] and is currently being studied in a phase 2a trial (ORION) for its impact on insulin sensitivity, liver enzymes, and liver imaging and a phase 2b trail (CENTAUR) for histological effects in patients with NASH and fibrosis.[37] Another immune modulator, amlexanox, is conversely a IKKε/TBK1 inhibitor found to

induce weight loss, improve insulin sensitivity, and decrease steatosis and expression of inflammatory genes in animals. A phase 2 study is currently examining the impact of the treatment on hepatic fat content by imaging in patients with diabetes, obesity, and NAFLD.[38] There are also emerging treatments that target the TNFα pathway, including pentoxifylline which showed improved survival in a subset of patients with alcoholic hepatitis and is currently in a phase 2 trail in NASH patients with and without cirrhosis.[39]

A third set of medications targets various pathways and processes in the gut that are involved throughout progression of the disease. For example, the anti-obesity agent orlistat could have promise as an adjunct to assist with weight loss in some patients.[40,41] Additionally, some medications could improve NAFLD and NASH prognosis by modulating the gut microbiome, including the macrolide antibiotic solithromycin which is not active against Gram-negative bacteria found in the gut and the IgG-rich extract of bovine colostrum IMM-124e.[1,12]

A final fourth subset of emerging medications targets various metabolic pathways specifically associated with fibrosis in the disease. For example, the antifibrotic simtuzumab, a monoclonal antibody targeting lysyl oxidase currently in a phase 2 trial in NASH patients with and without cirrhosis.[1] It is also important to note that several emerging drugs have molecular targets that play a role in multiple metabolic pathways. For example, the immune modular cenicriviroc dual targets CCR2/CCR5 have roles in metabolic pathways associated with both inflammation and fibrosis[36,37] while the PPARα/δ agonist elafibranor's dual targets are involved in multiple pathways, including liver fat accumulation, inflammation, and fibrosis.[30]

If proven successful, investigational treatments that target the different pathways associated with the disease could also be simultaneously used in future combination therapies.[12,16] Targeting multiple pathways at once could boost the overall impact of treatment and help improve prognosis in NAFLD and NASH patients. Indeed, initial steps are already being taken to examine the impact of combination therapies even before clinical approval of each involved pharmacotherapy. A phase 1 study of cenicriviroc in combination with evogliptin, a dipeptidyl peptidase-4 inhibitor previously studied in patients with diabetes, was recently announced to soon take place in healthy adult subjects to monitor safety and tolerability of the combination therapy.[15] More advanced trials of combination therapies for NASH are also in the clinical pipeline, including a phase 2 study with the ASK1 inhibitor GS-4997 alone and in combination with previously described monoclonal antibody simtuzumab.[16]

In addition to these numerous emerging pharmacotherapies, several recently approved surgical therapies can help patients struggling with weight loss. Endoscopic interventions and surgical approaches have already been shown to be effective at helping patients lose weight.[13] In particular, aspiration therapy and approaches with intragastric balloons show particular promise.[17]

It is critical to educate clinicians about these many new and emerging pharmacotherapies to help them stay abreast of the rapidly changing landscape for treatment of NAFLD and NASH. Improved awareness of these treatments may ultimately help clinicians select appropriate treatments and improve the outcome of their patients.

LEARNING OBJECTIVES

Upon completion of this activity, learners will:

- Recognize the prevalence of NASH in patients with NAFLD and what conditions put patients more at risk for the disease.
- Describe the latest published guidelines and recommendations on the screening and diagnosis of NAFLD and NASH.
- Review on the latest published guidelines and recommendations for the treatment of NASH.
- Define the pathogenesis of NASH and how new and emerging pharmacotherapies aim to target various metabolic pathways involved in disease progression.
- Implement new advances in surgical treatments for NASH that can help promote weight loss.

Clinical/Practice Gap	Educational Need	Learning Objective That Will Address the Gap and Need	Result(s) that will be measured	Type of Gap That Will Be Met	ACGME Competencies That Will Be Met
NAFLD and NASH often progress silently, making it difficult for clinicians to identify patients with the disease.	Clinicians need to recognize the prevalence of NASH and the many risk factors associated with the disease to help them identify and diagnose patients. Clinicians also need to recognize and follow published screening and diagnostic guidelines.	Recognize the prevalence of NASH in patients with NAFLD and what conditions put patients more at risk for the disease.	1) Ability to meet learning objectives as measured by post-activity evaluation 2) Changes in responses to case vignette questions 3) Intention to make practice changes as indicated on post-activity evaluation	Competence	Medical Knowledge Problem based learning and improvement Medical Knowledge Problem based learning and improvement
Clinician management of NASH often diverges significantly from published guidelines.	Clinicians need to be up-to-date with the most recent management guidelines for NADLF and NASH.	Describe the latest published guidelines and recommendations on the screening and diagnosis of NAFLD and	1) Ability to meet learning objectives as measured by post-activity evaluation 2) Changes in responses to case vignette	Competence	Medical Knowledge Problem based learning and improvement

		NASH. Review on the latest published guidelines and recommendations for the treatment of NASH.	questions 3) Intention to make practice changes as indicated on post-activity evaluation		
There is a current significant lack of management strategies for NAFLD and NASH.	Clinicians need to be aware of new advances in the disease pathogenesis of NASH to help them navigate the wealth of new and emerging treatment strategies that are poised to alter the treatment landscape.	Define the pathogenesis of NASH and how new and emerging pharmacotherapies aim to target various metabolic pathways involved in disease progression. Implement new advances in surgical treatments for NASH that can help promote weight loss.	1) Ability to meet learning objectives as measured by post activity evaluation 2) Changes in responses to case vignette questions 3) Changes in level of knowledge as measured by pre and post-assessment knowledge based questions	Competence	Medical Knowledge Problem based learning and improvement

AGENDA

5 minutes **Activity overview**
Pre-activity assessment

10 minutes **Identifying NASH in Cardiometabolic Patients: Prevalence and Risk Factors**
--Risks of NASH (understanding why it is important to identify and treat)
--Prevalence
--Risk factors

10 minutes **NASH Pathogenesis**

20 minutes **Diagnosing NASH**
--2012 Guidelines
--Diagnostic strategies

--Genomic approaches

30 minutes **Current Treatments and Treatments on the Horizon**
--Genetically tailored treatment
--Current treatment recommendations
--Emerging treatments

10 minutes **Case Studies**

Case study #1:
A 70-year-old man is suspected to have ascites after examination during a routine physical with his PCP. He presents with abdominal pain, discomfort, and shortness of breath. Subsequent bloodwork detects elevated liver enzyme levels (aspartate aminotransferase [AST] 80 U/L, alanine aminotransferase [ALT] 91 U/L). The patient has previously been seen for prediabetes and has a body mass index of 33.2. He is diagnosed with NASH with mild cirrhosis using a liver ultrasound and is referred to a hepatologist.

- What factors made this patient more at risk for NASH and NAFLD?
- What's the appropriate way to diagnose NASH?

The hepatolgoist confirms diagnosis with a liver biopsy and prescribes 800 IU/day of vitamin E.

- What concerns, if any do you have about the patient's medication regimen given his background and diagnosis?
- What potential change(s) would you make to his medication regimen? Why?

Case study #2:
A 50-year-old female with a BMI of 28 has a family history of cardiometabolic disease and completes regular screening and checkups with a cardiologist. During a routine visit, slightly elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (AST) are detected. A liver ultrasound followed by a biopsy leads to the diagnosis of NASH with no fibrosis.

- What are the best treatment options for this patient? Are lifestyle changes appropriate? Vitamin E? Pioglitazone? Why or why not?
- What else would you recommend for this patient given her family history of cardiovascular disease? Are statins appropriate?

During a checkup a year later, the patient expresses concern that she has been struggling to lose the recommended 3-5% of her body weight despite maintaining a healthy diet and regularly exercising.

- What other new or emerging options can help patients like her with initial or sustained weight loss?

- Is she a good candidate for these options?

5 minutes **Conclusions**
Post-activity assessment

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