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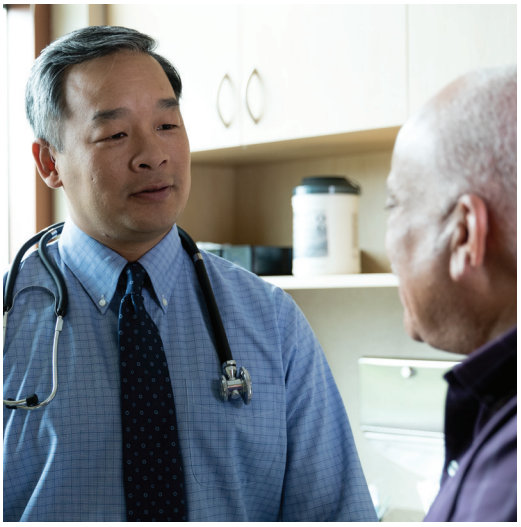
OptumCare Forum for Evidence-Based Medicine

November/December | 2018

EDUCATIONAL FORUM

Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis (NAFLD/NASH)[1,2]



Introduction – Now that close to 70% of Americans are overweight or obese, NAFLD has become the most common chronic liver disease in the US, representing ~75% of all cases. The annual direct cost attributable to NAFLD/NASH in the US exceeds $100 billion. However, because a large proportion of these patients also have the metabolic syndrome, it is still cardiovascular disease and not chronic liver disease that is the most common cause of death in these patients. It is estimated that 30% of the US population has NAFLD and 5% has NASH; which is the next step in the evolution towards cirrhosis. Cirrhosis due to NASH will ultimately occur in 2% of the American population and will soon become the most common reason for liver transplantation. NASH is defined by the presence of hepatocyte damage with inflammation. The progression of NAFLD to NASH is linked to insulin resistance causing accumulation of toxic lipid metabolites and activation of inflammatory mediators, including TNF alpha. There may also be important contributions from an abnormal gut microbiome. Histologically, NASH is indistinguishable from alcohol related liver damage. Importantly, the most potent risk factors that predict the transition from NAFLD to NASH are Type 2 diabetes and the various components of the metabolic syndrome. The risk of hepatocellular carcinoma is similar to that from other causes of cirrhosis; therefore patients with cirrhosis need yearly ultrasound surveillance for the development of hepatocellular carcinoma (HCC).

Diagnosis – Since it is impractical to perform liver biopsy on all patients with NAFLD, obtain an ultrasound for initial evaluation. Ultrasound has a sensitivity of 85% and a specificity of 94% for the diagnosis of NAFLD. The following studies will exclude the vast majority of other alternative diagnoses.

- Iron studies for hemochromatosis
- Hepatitis B and C serologies for chronic viral hepatitis
- ANA and anti-smooth muscle antibody for autoimmune hepatitis
- Anti-mitochondrial antibody for primary biliary cirrhosis
- Alpha-1 antitrypsin level for alpha-1 antitrypsin deficiency

Because alcohol excess causes identical histologic changes, it may be either the primary etiology or contributory depending on the level of alcohol intake. Moderate alcohol intake at one to two drinks daily has not been found to cause or adversely affect NAFLD.

Although the specificity of an elevated alanine aminotransferase (ALT) level for the diagnosis of NAFLD is 85%, the sensitivity is only 45% and patients can progress to cirrhosis with normal liver function tests (LFTs). The AST/ALT ratio is typically < 1. Clinical signs suggesting the progression to cirrhosis include progressive elevations of the AST/ALT with a ratio >1, increased bilirubin levels, thrombocytopenia, or exam stigmata of advanced liver disease.

(continued on page 2)

Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis (NAFLD/NASH)

(continued from page 1)

The NAFLD fibrosis score (NFS) is a validated tool to predict liver related outcomes and uses readily available clinical data. A level less than -1.45 excludes advanced fibrosis and a level above 0.67 suggests advanced fibrosis. This can be used to determine the subset of patients who will benefit from GI referral for possible biopsy.

Management – Pharmacotherapy is not recommended in the absence of NASH. There are no FDA approved drugs, and the best data to date show improvements in only ~50% of patients with any intervention other than weight loss. There is ample data to support weight loss to reverse NAFLD/NASH and since there are available therapies for this, including drugs and bariatric surgery, weight loss should be considered the cornerstone of treatment. Additionally, Type 2 diabetes should be aggressively managed. Low carb diets have shown greater improvement in NAFLD compared to other types of diets. Bariatric surgery in 766 patients with paired liver biopsies showed improvement in NAFLD in 91%, NASH in 81%, and fibrosis in 65% of patients.

- **Vitamin E** at a dose of 800 IU daily has been shown in a randomized trial to improve both liver tests and histologic changes of both NAFLD and NASH including resolution of NASH in 36% of patients. However, fibrosis scores were not improved with Vitamin E treatment.
- Importantly, **Metformin** improves insulin sensitivity but has not been shown to improve liver histologic changes. This may be related to the fact that its main effects are on increasing muscle uptake of glucose and decreasing hepatic glucose production, with lesser effects on fat metabolism. If however, patients treated with metformin have significant weight loss and/or improvement in Type 2 diabetes, liver function is likely to secondarily improve.
- **Pioglitazone** also improves insulin sensitivity and is the best studied of the pharmacologic agents and has demonstrated clear benefits. This may be related to the fact that unlike metformin, pioglitazone improves adipocyte function, and thus increases fatty acid uptake in adipose tissue, decreasing the fatty acid load to the liver and thereby decreasing deposition of fat in the liver. This improves insulin sensitivity at the expense of the expansion of peripheral fat mass (thus the weight gain seen with this drug class). Improvements in the 35-50% range in liver functions and histologic changes have been seen in both diabetic and non-diabetic populations with the use of pioglitazone. The number needed to treat with pioglitazone for resolution of NASH ranges from 2-12, which makes it a reasonable treatment strategy.
- Phase II trials have shown improvements in NASH using the **GLP-1 agonist** class and phase III trials are ongoing. Smaller trials have shown benefits using probiotics and fish oil supplements, both of which have been shown to improve insulin sensitivity.
- Lastly, there are small trials showing benefits, including improved histologic changes with use of **pentoxifylline** which is a TNF alpha antagonist.

Summary – We are likely to be under diagnosing both NAFLD as well as NASH. Increased vigilance is required to identify the subset of our patients with NAFLD who are progressing towards NASH and cirrhosis. Once identified, the first efforts should be directed at lifestyle including, when indicated, pharmacologic approaches to weight loss. Additionally, when present, this includes optimal control of Type 2 diabetes. If unsuccessful, the options are to initiate supplement therapies using probiotics, Vitamin E, and/or fish oils, versus initiation of pharmacotherapy using pioglitazone. Bariatric surgery has a clear role when obesity is resulting in the progression of NAFLD to NASH and cirrhosis. NAFLD progressing to cirrhosis will likely be the most common form of cirrhosis and the most common reason for liver transplantation in the near future.

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2. Stafan, N., Haring, H.-U., & Cusi, K. (2018). Non-alcoholic fatty liver disease: Causes, diagnosis, cardiometabolic consequences, and treatment strategies. The Lancet Diabetes and Endocrinology(18), 1-12. doi:10.1016/

Decreasing Antibiotic Utilization

There are few circumstances in daily practice where a single drug class may simultaneously be lifesaving, life threatening, and seriously misused. In an ideal world, antibiotics would be safe enough that intense prescribing scrutiny would not be needed. Unfortunately, this is clearly not the case. Antibiotic toxicity falls generally into four categories:

1. Antibiotic resistance which impacts both public health as well as the likelihood that any patient will suffer the consequences of an inadequately treated infection due to a resistant organism.
2. Alterations in the gut microbiome which can range from life threatening C. difficile infection down to transient or persistent diarrhea. C. diff infections are becoming increasingly severe, resistant, and more difficult to treat.
3. Direct toxicity such as the tendinopathy and neurotoxicity of quinolones and the vestibular and renal toxicity of the aminoglycosides.
4. Idiosyncratic and/or allergic drug reactions which may be dermatologic or systemic and may be severe and life threatening.

Given this conundrum, are there circumstances where antibiotic utilization may be more targeted to the clinical circumstances where the benefits exceed the risks? Existing as well as emerging data call for a closer look at antibiotic indications related to the following clinical scenarios.

Acute Diverticulitis

The standard of care for decades has been antibiotic treatment, but surprisingly there is a paucity of data to support this approach. There are now two randomized trials of CT confirmed uncomplicated acute diverticulitis and both trials showed no improvement at one year of follow-up when antibiotic therapy was compared to observation.[3,4] The larger and more recent trial, DIABOLO Trial [5] looked at over 500 patients with an uncomplicated first episode of left sided acute diverticulitis and randomized them to observation versus amoxicillin/clavulanic acid for 10 days, with the first two days as IV therapy. Recovery rates were similar, and the rates of hospitalization, complicated diverticulitis, and sigmoid resection did not statistically differ between the two groups. There was however, a non-significant trend towards more cases of complicated diverticulitis and sigmoid colon resection with observation in both of these trials and therefore the DIABOLO Trial followed these patients for an additional year and recently reported the results at two years of follow-up. At two years of follow-up, the findings included:

- Recurrence rates were virtually identical in both groups at 15%.
- No statistical differences in the occurrence of complicated diverticulitis or the need for emergency surgery.
- Slight increase in the number of elective sigmoid resections in the observation group. This last point is difficult to explain since the recurrent rate was identical in both groups. The treating physicians were not blinded to the study arm and it is therefore possible that the physicians had a lower threshold to operate in the placebo group.
- 8.3% of the antibiotic treated patients experienced morbidity related to antibiotic treatment.

Given these data, how should this inform our use of antibiotic therapy for acute uncomplicated diverticulitis? When faced with a patient presenting with an acute, painful, febrile episode of LLQ pain and associated CT confirmation of acute diverticulitis, we will likely feel compelled, albeit without supporting evidence, to treat with antibiotic therapy. However, the more common scenario we encounter is mild diverticulitis, or more importantly LLQ pain without fever or leukocytosis which is often presumed to be mild diverticulitis. We should use the above studies to feel comfortable in not treating with antibiotics in these patients, understanding that the literature supports a greater likelihood of harm than benefit. We should also feel comfortable that even if a case of mild LLQ pain is attributed to functional disease such as IBS, that no harm would be done in the case of a missed diagnosis of mild diverticulitis since antibiotics should not have a role in treating this. Lastly, given the absence of data supporting the need for antibiotics in acute diverticulitis, unless complicated diverticulitis is suspected, there should be fewer indications for CT scanning with a significant decrease in radiation exposure and cost to our patients.

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Bacterial Cellulitis

Stasis cellulitis is often misdiagnosed as bacterial cellulitis and is thus a common cause of inappropriate antibiotic utilization. Two recent studies in JAMA Dermatology [6,7] prospectively evaluated patients in the ED or hospital who were admitted with a presumptive diagnosis of bacterial cellulitis. Dermatology consultation was obtained in each patient in both studies and the dermatology consultant made a diagnosis other than bacterial cellulitis in about a third of the cases. Antibiotics were discontinued in these patients with no adverse consequences. The most frequent admitting diagnosis in these cases was stasis cellulitis. Stasis cellulitis is more frequently bilateral, is associated with less tenderness, and not associated with fever or leukocytosis. Antibiotics are not indicated in stasis cellulitis.

Acute Viral Respiratory Illness

No discussion of appropriate antibiotic utilization would be complete without focusing on the unfortunate continued use of antibiotics for viral respiratory illness. There are multiple studies supporting the avoidance of antibiotics in this situation. Despite the surfeit of literature, an astounding rate of inappropriate use persists. This was most recently highlighted in a study in JAMA Infectious Disease [8] Over 14,000 patients were studied during the 2013-2015 influenza seasons. 41% of patients received an antibiotic prescription and 41% of those patients had diagnosed viral URI or viral bronchitis. 30% of patients with confirmed influenza also received an antibiotic prescription. Of the patients given antibiotics for pharyngitis, 38% were given a prescription after a negative GAS test. Additionally, 38% of the patients given an antibiotic prescription for sinusitis had symptom duration of three days or less. As a profession, we continue to do harm to patients with viral respiratory illness and we need to be collectively and individually responsible for correcting this deficiency.

Glutamine for Postinfectious IBS

Post infectious diarrhea following a bout of enteric infection is common and represents a transient, although often prolonged form of IBS. Treatment options for this have been limited and without a strong evidence base of support. A small but impressive trial [9] was recently published, where 106 patients were randomized to OTC glutamine 500 mg TID versus placebo for eight weeks. Improvement occurred in 80% of the glutamine group and 6% of the placebo group. There were no adverse effects related to the use of glutamine. Pending the results of larger trials, given the efficacy, safety, and low cost, this would be a reasonable treatment strategy to employ.

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8. Avers, F. P., Hicks, L. A., & Chung, J. R. (2018). Outpatient antibiotic prescribing for acute respiratory infections during influenza seasons. JAMA Network Open, 1(2). doi:10.1001/jamanetworkopen.2018.0243

9. Zhou, Q., Verne, M. L., Fields, J. Z., Lefante, J. J., Basra, S., Salameh, H., & Verne, G. N. (2017). Randomised placebo-controled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. Neurogastroenterology. doi:10.1136/gutjnl-2017-315136

Cost effective management of Type 2 diabetes: Insulin Analogs – The "New" versus the "Old"

The "new" basal insulin analogs have largely replaced the use of NPH insulin at more than ten times the cost. New data suggests that there are not substantial benefits to these insulins despite the exorbitant costs, which challenge our patients' ability to pay for them.

The first study [10] was a retrospective study of the large Kaiser Health plan data base and looked at the risk of an ER visit for hypoglycemia as well as overall levels of A1c control within one year of initiating either a new insulin analog or NPH insulin in over 25,000 patients. The rate of severe hypoglycemia necessitating ER visit or admission was lower in the NPH group by about 25%, although the absolute risk was low in both groups. Likewise, the overall A1c control was better in the NPH group (8.1% in the new analog group and 7.9% in the NPH group).

The second study [11] was a meta-analysis of Thirty-nine trials in over 26,000 patients. Comparing all new basal analogs with NPH showed equivalent glucose lowering effects, no significant differences in the rate of severe hypoglycemia and only a mild reduction in the rate of nocturnal hypoglycemia with the longer acting newer insulin analogs compared to the older basal analogs and NPH.

Given the new ACP guideline suggesting a lowering of treatment intensity in most adults with Type 2 DM, the data from these two trials suggests that our patients may do just as well and perhaps better, using generic NPH insulin at one tenth the cost of the newer agents. **Each CDO may want to consider a systematic approach for converting the appropriate patients to generic NPH at a cost of $25/vial, which would be about one twentieth the cost compared to a branded agent for a patient on 50 units of basal insulin daily.**

Benign Paroxysmal Positional Vertigo (BPPV) – Algorithm for Prediction of Diagnosis

BPPV is the most common form of vertigo and may be misdiagnosed as vertigo of central origin or due to vertebrobasilar insufficiency. This may result in unnecessary referrals, ER evaluations or imaging of the posterior circulation. Since isolated vertigo is a symptom of vertebrobasilar insufficiency in under 1% of cases, it would be useful to have a highly accurate diagnostic algorithm to help establish the diagnosis of BPPV such that ENT/neurology referrals, ER evaluations and unnecessary imaging may be avoided. Such a diagnostic algorithm was developed in 2016 and recently prospectively tested in 200 patients presenting to a university ENT department for dizziness or vertigo.[12] Use of the algorithm was 75% sensitive and 100% specific such that no patient diagnosed using the algorithm had an alternative etiology for their symptoms. As expected, the features which correlated with BPPV were:

- Vertigo described as lasting seconds as opposed to minutes, or longer
- Vertigo triggered by lying down or rolling over in bed
- The absence of tinnitus, hearing loss, or headache associated with the vertigo

Vertigo symptoms meeting these criteria should be treated with Canalith Repositioning and/or vestibular rehabilitation prior to referral or imaging.

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12. Britt, C. J., Ward, B. K., & Owusu, Y. (2018). Assessment of a statistical algorithm for the prediction of benign paroxysmal positional vertigo. JAMA Otolaryngology Head and Neck Surgery. doi:10.1001/jamaoto.2018.1657

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Chief Medical Officer

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

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