WELCOME TO
AK LIVER DISEASE ECHO

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

NPAIHB
Indian Leadership for Indian Health

This project is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

PLEASE PUT IN THE CHAT BOX:

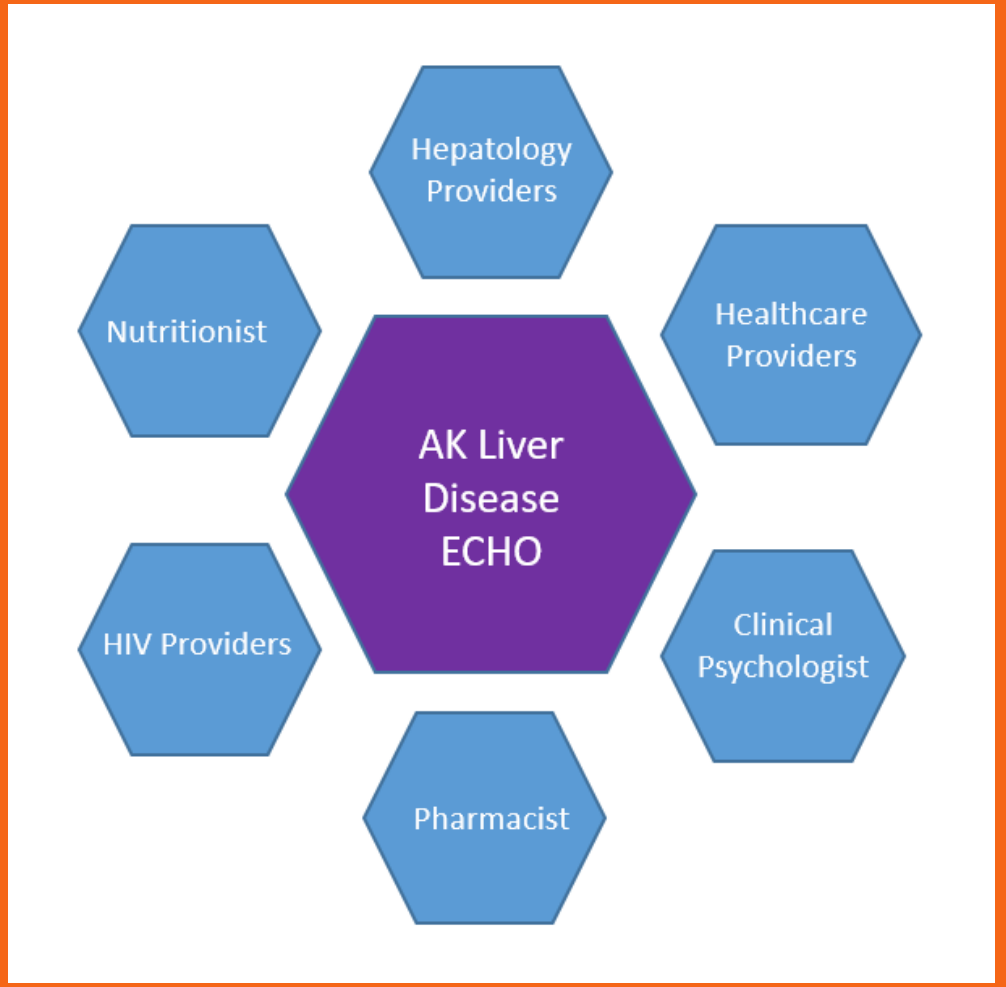
Your name
Where you are located
What brings you to the LD ECHO today

WHAT WE DO

- Didactic Presentations pertaining to ECHO topics
- We're accepting **case presentations and questions pertaining to:**
  - Elevated Liver Function Tests
  - Cirrhosis
  - Managing Complications of Decompensated Cirrhosis – Ascites, encephalopathy, esophageal varices
  - Alcohol-related liver disease, including Alcohol Hepatitis
  - Autoimmune liver disease – Autoimmune Hepatitis, Primary Biliary Cholangitis, Overlap
  - Nonalcoholic fatty liver disease/Nonalcoholic steatohepatitis
  - Hepatocellular carcinoma
- Provide Expert Panelists

CONSULTANT TEAM

- Brian McMahon, MD Hepatologist
- Youssef Barbour, MD Hepatologist
- Lisa Townshend, ANP Hepatology Provider
- Annette Hewitt, ANP Hepatology Provider
- Leah Besh, PA-C HIV/Hepatology Provider
- Anne Fleetwood, MS, RDN, NDN
- Brittany Keener, PharmD, MPH, BCPS
- Kena Desai, MD, Internal Medicine Specialist



Welcome to Alaska Liver Disease ECHO

Approved Provider Statements:

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Alaska Native Medical Center (ANMC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Contact Hours:

ANMC designates this activity for a maximum of 12 contact hours, including 3 total pharmacotherapeutics contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

To receive CE credit please make sure you have actively engaged in the entire activity, your attendance is recorded by the facilitator, and complete the course evaluation form found here: https://forms.gle/R8vibUZgMbRcoScw9.

For more information contact
jlfielder@anthc.org or (907) 729-1387

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

LIVER DISEASE ECHO SCHEDULE AT A GLANCE

- **April 21st – Future Drugs for NALFD**
- May 19th – Hepatitis B and other Vaccine Updates
- June 16th AIH in AN/AI Population in Alaska
- July 21st – PBC/Overlap
- August 18th – Most Common Liver Toxic Drugs
- September 15th – Trauma Informed Care and Liver Disease
- October 20th – Screening for Alcohol Use Disorder

LAND ACKNOWLEDGEMENT

Out of great respect, we acknowledge the Creator of all living things and the original inhabitants upon whose traditional lands we respectively now gather or reside.

Let us, forever, remember the benefits and bounty of the vast resources that stem from these traditional lands, and thank the original inhabitants for their past and present stewardship of the resources (i.e., waters, plants, animals), and the spiritual practices which they cherish on the lands we now call home.

Updates in NASH Treatment

Youssef Barbour, MD

No conflict of interests to disclose for this presentation

Pre-didactic Question

In the future, the most promising treatment for NASH will likely be:

A. PPAR agonists
B. Thyroid hormone receptor agonists
C. Farnesoid X receptor agonists
D. Combination treatments

Current FDA approved treatments for NASH

- 1- Pioglitazone
- 2- Vitamin E 400 IU BID in non-diabetic non-cirrhotic patients.

Why is it taking so long to find new therapeutics?

- 1- Therapeutic endpoints
- 2- Patient selection and cost effectiveness

Therapeutic Endpoints

- The primary purpose of treatments for NASH is to: reduce morbidity and mortality from liver disease. Therefore, in terms of defining the efficacy of treatment the "hard" clinical endpoints in NASH consist of all-cause mortality, liver-related mortality, and liver decompensation events.
- It is notable that the first successful trials of medical therapy to reduce cardiovascular disease mortality were in secondary prevention, whereas **the majority of efforts in therapeutic trials in NASH are in non-cirrhotic population as primary prevention of liver-related morbidity and mortality.**
- In that context it is anticipated that the proportion of patients with non-cirrhotic NASH who will develop a hard clinical endpoint in the short-term is *low*…
- So: the regulatory agencies in the US and Europe have agreed on **histologic surrogate endpoints that will allow both early and late assessment of efficacy**

Early Histologic Endpoints Considered Reasonable Likely to predict Clinical Benefit in Phase 3 Trials in Non-cirrhotic NASH

FDA

- **-Resolution of NASH without worsening of fibrosis OR**
- **-Improvement of fibrosis (equal or > 1 stage) without worsening of NASH**

  OR
- **-Both**

European Medicines Agency

- Resolution of NASH **AND** improvement of fibrosis (equal or > 1 stage)

Patient Selection, Clinical and Cost Effectiveness

- When considering the role of treatment, the absolute risk of liver-related morbidity and mortality in these patients must be considered. Therefore the broad acceptance is that patients with **NASH and stage 3 fibrosis are the more attractive group of patients who might benefit from a pharmacologic therapy if it is effective in slowing the progression of disease to cirrhosis, and reduce liver related morbidity and mortality.**
- It is foreseeable that the **cost-effectiveness and societal benefit would be higher in those with NASH with stage 2 or higher fibrosis, particularly in those with bridging fibrosis and cirrhosis because of the higher risk of liver-related events in patients with advanced fibrosis.**
- With interest in identifying the so-called fast progressors at early stage of fibrosis.
- For identifying those patients, and monitoring them, **liver biopsy** remain an essential tool.

Rowe, I, Wong, V., Loomba, R. Treatment Candidacy for Pharmacologic Therapies in Nash. Clinical Gastro and Hep 2021. https://doi.org/10.1016/j.cgh.2021.03.005

Patient selection for inclusion into a clinical trial by noninvasive tests

Early phase trials

- Most trials apply a pre-screening strategy with CAP ≥to 300 db/min to maximize the likelihood that patients will meet the MRI-PDFF >8% as an inclusion criterion used in most early phase trials

Late phase trials

- Phase 2b and phase 3 trials in NASH now typically enroll those patients most in need of treatment for NASH, these trials require a liver biopsy assessment at baseline.
- Various types of strategies have been used to screen for patients that meet criteria to enrich the cohort.
- In a recent study, Jung et al demonstrated that MRE equal or more than: 3.3 kPa and FIB-4 equal or more than 1.6 are associated with 97% positive predictive value for stage equal or more than 2 fibrosis

Current NASH medications in phase 3 clinical trial

- 1- **Obeticholic Acid**: Farnesoid X receptor agonist (REGENERATE)
- 2- **Elafibranor**: Peroxisome Proliferator-activated receptor-alpha and –delta agonist (RESOLVE-IT)
- 3- **Cenicriviroc**: inhibitor chemokine receptors 2 and 5 (AURORA)
- 4- **Resmetiron**: Thyroid hormone receptor-beta agonist (MAESTRO-NASH)
- 5- **armachol**: a bile acid and fatty acid analogue (NCT02279524)

- In contrast, **selonsertib**, an apoptosis signal-regulating kinase-1 (ASK1) antagonist, failed to demonstrate any effect on NASH or fibrosis in the phase 3 STELLAR studies

NASH meds in PHASE 2 clinical trials

Similar mechanisms

- -a few more Farnesoid X receptor agonists
- -a few more PPAR agonists
- -one more thyroid hormone receptor-beta agonist

Different mechanisms

- *-GLP-1 agonists*
- *-FGF 21 analogue*
- *-FGF 19 analogue*
- *-Acetyl-CoA carboxylase inhibitor*
- *-Mitochondrial pyruvate carrier inhibitor*

Other drugs in study from AASLD The Liver Meeting® 2021

- ***Ileal bile acid transporter inhibitor***.
- -indicated to treat pruritus by reducing levels of bile acids in circulation
- ***Retinoic acid receptor beta2 agonist***
- -based on NAFLD patients commonly presenting loss of vitamin A and its metabolites in the liver
- ***SGLT2 inhibitor***
- -established DM II treatment

A systematic review and network meta-analysis, abstract from AASLD 2021

- Abstract from Donald and Barbara Zucker school of Medicine, NY USA.
- A thorough systematic review and frequentist random effects network meta-analysis was performed across all randomized clinical trials reporting a phamacotherapeutic intervention on adult patients with biopsy-proven NASH
- 6533 total studies were identified via a thorough literature search and systematic review, after removing duplicates and adhering to the exclusion criteria, a total of 40 RCTs were identified including 6593 total patients with biopsy-proven NASH
- The most effective and statistically significant treatment interventions for primary end points were as follows:

1- Minimum 2 point improvement in NAFLD activity score

- 1- aldafermin 1mg
- 2- vitamin E 800 IU in combination with pioglitazone 45 mg
- 3- pioglitazone 45 mg
- 4- resmetiron 80 mg
- 5- obeticholic acid 25 mg, and 10 mg

2-NASH resolution without worsening fibrosis

- 1- aldafermin 1 mg
- 2- pioglitazone 45 mg
- 3- vitamin E 800 IU in combination with pioglitazone 45 mg
- 4- pioglitazone 30 mg
- 5- vitamin E 800 IU
- 6- obeticholic acid 25mg

3- Improvement of fibrosis without worsening NASH

- 1- Obeticholic acid 25 mg and 10 mg

4- Improvement in Fibrosis

- 1-Obeticholic acid 25 mg

NASH treatment

- -Lifestyle intervention to lose weight, targeting 10% of body weight, through diet and exercise remains the cornerstone of treatment for NAFLD/NASH
- -Because the response rate to individual drugs has so far been modest, it is anticipated that combination treatment will likely be required, and the field needs robust methods to determine whether a patient is responding to treatment.

Thank you

Post Test Question

In the future, the most promising treatment for NASH will likely be:

A. PPAR agonists
B. Thyroid hormone receptor agonists
C. Farnesoid X receptor agonists
D. Combination treatments

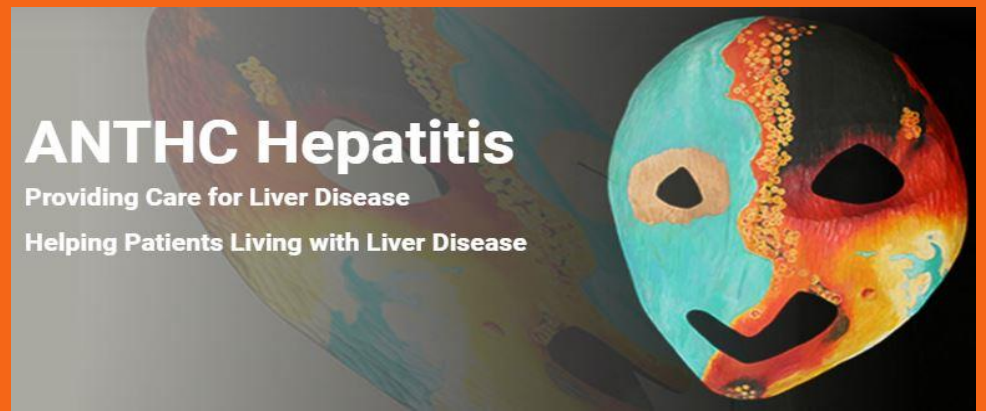
Post Test Question

In the future, the most promising treatment for NASH will likely be:

A. PPAR agonists
B. Thyroid hormone receptor agonists
C. Farnesoid X receptor agonists
D. **Combination treatments**

ADDITIONAL LEARNING OPPORTUNITIES

- AK ID ECHO: HCV, HIV, PrEP, STIs
  - The 2nd Tuesday of every month from 12:00-1:00PM Alaska Standard Time
    - 1CE/CME offered per session
  - anthc.org/project-echo/hcv-hiv-prep-stis-echo
- LiverConnect Webinar Program
  - Second Tuesday of every month 8:00-9:00AM Alaska Standard Time
    - Full Hour didactic topics on Liver Disease and related topics 1CE/CME offered
  - anthc.org/what-we-do/clinical-and-research-services/hep/liverconnect/



AK LIVER DISEASE ECHO -TEAM CONTACTS

- Lisa Townshend-Bulson, MSN, FNP-C, Program Manager, ltownshend@anthc.org
- Marla Wehrli, Program Coordinator, mjwehrli@anthc.org
- Wileina Rhodes, RN Nurse CE Coordinator, wsrhodes@anthc.org
- Annette Hewitt, FNP-C Pharmacology Content Reviewer, amhewitt@anthc.org
- Cindy Decker, RN Liver Disease ECHO Nurse Case Manager, cadecker@anthc.org
- ANTHC Liver Disease and Hepatitis Program: 907-729-1560
- Northwest Portland Area Indian Health Board
  - David Stephens: Director Indian Country ECHO, dstephens@npaihb.org
  - Jessica Leston: Clinical Programs Director, jleston@npaihb.org

Thank you

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

NPAIHB
Indian Leadership for Indian Health

This project is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.