WELCOME TO
AK LIVER DISEASE ECHO

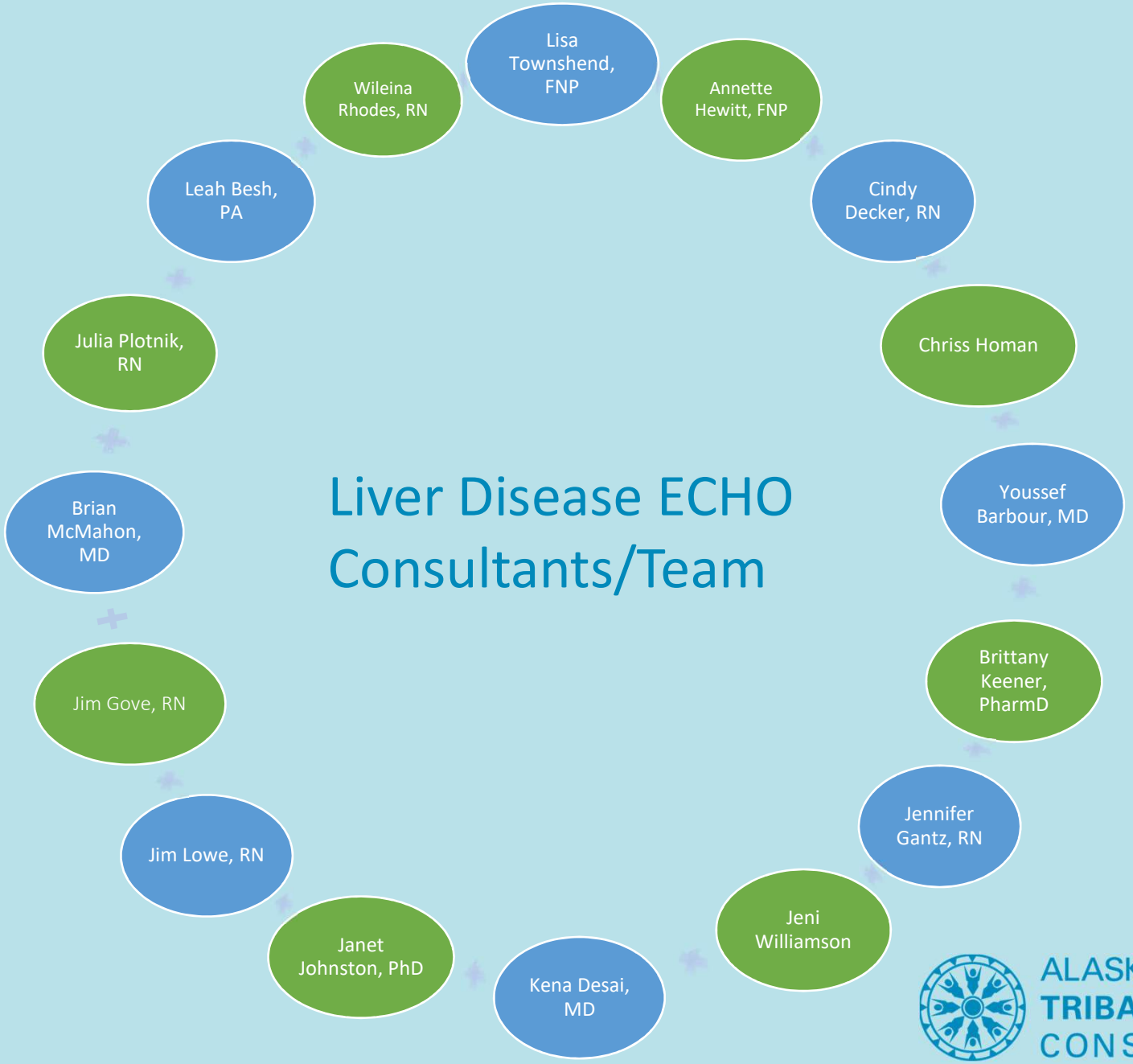
ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

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.

What we do

- Provide education related to liver disease management
  - Didactic presentations
  - Patient case presentations and questions
  - Expert panelist case review
- 2023 Theme: How You Can Help Reduce Liver Disease Mortality and Morbidity
  - addressing challenges to HCV screening and linkage to care
  - screening for metabolic associated fatty liver disease
  - managing cirrhosis
  - safe medication prescribing, and
  - nutrition for liver health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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.

CPE Credit will be posted to the online CPE Monitor system within 60 days following completion of each activity when applicable.

The ANMC Joint Accreditation CE Program Portfolio additionally supports Behavioral Health (APA), Social Work (ASWB-ACE), and Dietitians (CPEU).

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; Anne Fleetwood, faculty for this educational event, is a contractor with Tandem Diabetes Care. All of the relevant financial relationships listed for these individuals 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

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ALASKA NATIVE MEDICAL CENTER

Autoimmune Hepatitis: Update 2023

Brian McMahon, MD

Liver Disease and Hepatitis Program

Alaska Native Medical Center

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CONSORTIUM

Disclosures and Conflicts of Interest

- None

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Goals and Objectives

- To understand the epidemiology of autoimmune hepatitis (AIH) in the Alaska Native Population
- To understand the ways patients with AIH can present
- To understand the laboratory tests to obtain to help make the diagnosis of AIH
- To understand general principles of treatment and monitoring of AIH

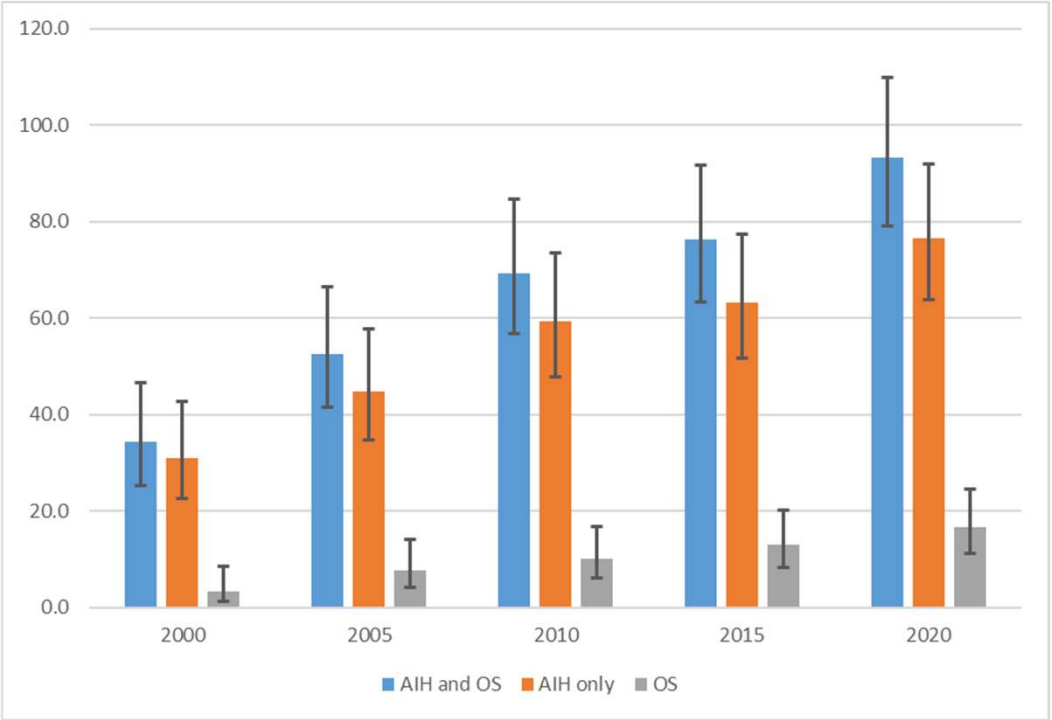
Quiz: Select the Best Answer

1. AIH has a bad outcome, even on treatment most persons will expire in 5-10 years
2. AIH only occurs after age 30
3. Women have a slightly higher prevalence of AIH
4. Remission can occur in up to 90% of persons
5. Liver biopsy is not helpful in AIH diagnosis

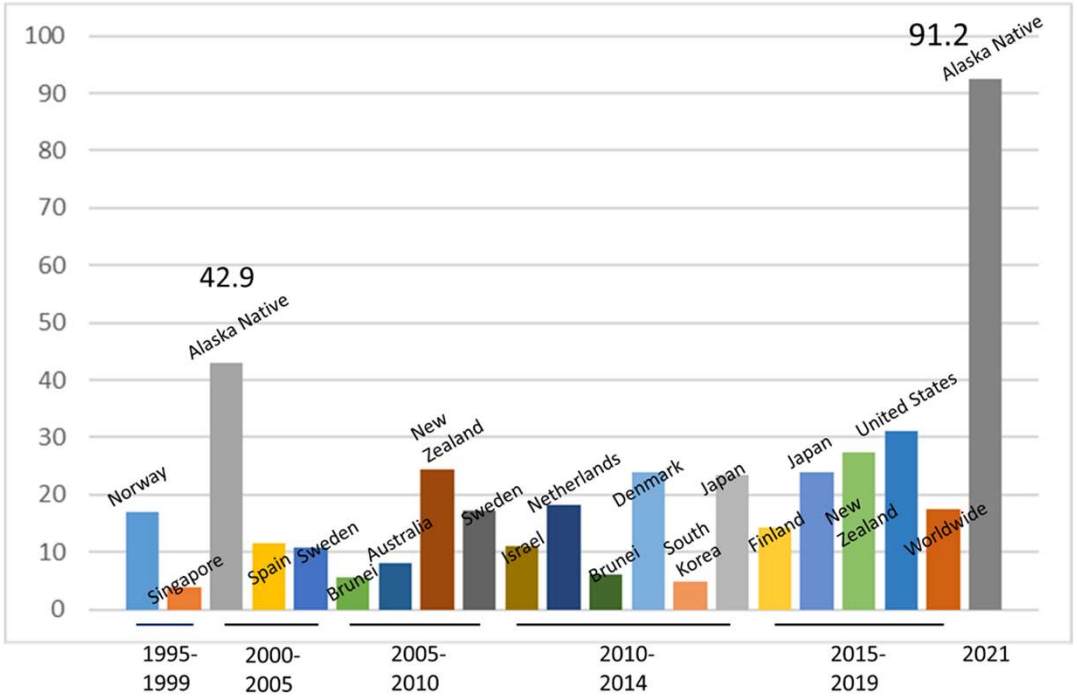
Autoimmune Hepatitis (AIH)

- Immune-mediated Inflammatory liver disease
- Affects all ages, genders, races/ethnicities
  - Highest documented prevalence in Alaska Native population
- 10% to 20% also have Primary Biliary Cholangitis (PBC) or Overlap Syndrome (OS)
- MASLD (NAFLD) features present in 17% to 30% of AIH patients
  - MASLD and/or heavy alcohol usage can accelerate liver damage
  - Mayo Clinic studies from the 1950's found that up to 70% untreated patients can die of liver failure in 2 to 3 years after diagnosis

AIH/OS Prevalence among AN People



AIH Prevalence across Time and Place



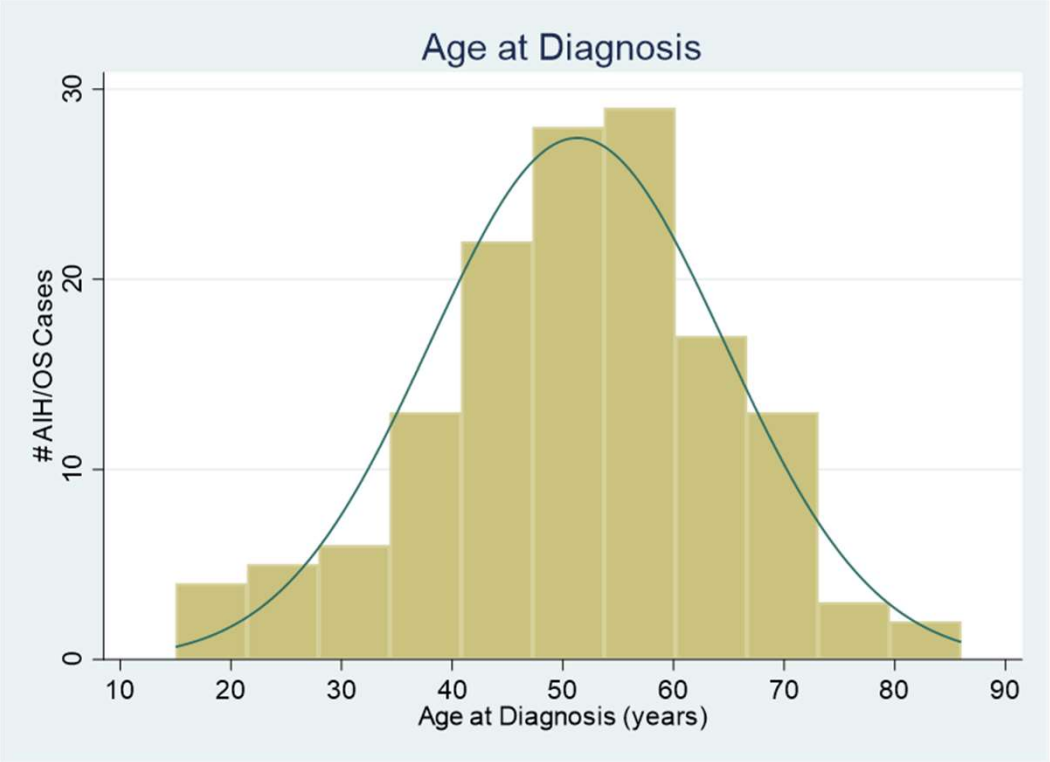
2019 Guidelines for AIH from the Liver Society: AASLD

- Download at aasld.org
- Then click on Practice Guidelines and select Autoimmune Hepatitis

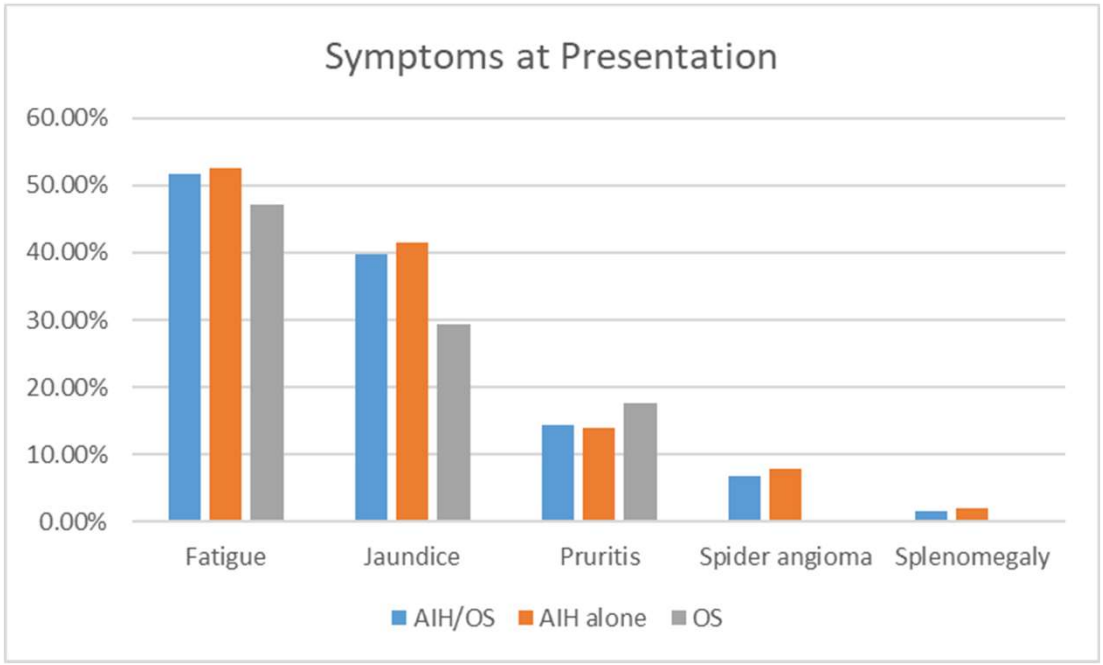
Demographics found in Alaska Native Peoples

- "Female predominance occurs in adults (71% to 95% women) and children (60% to 76% girls)"
  - AN AIH/OS: 91.5% female
    - AIH alone: 92.6%
    - OS: 8.5%
- "AIH occurs at all ages and within all ethnic groups"
- Fatty liver identified in 43% of AN people with AIH/OS

Age Distribution in AN AIH/OS Cohort

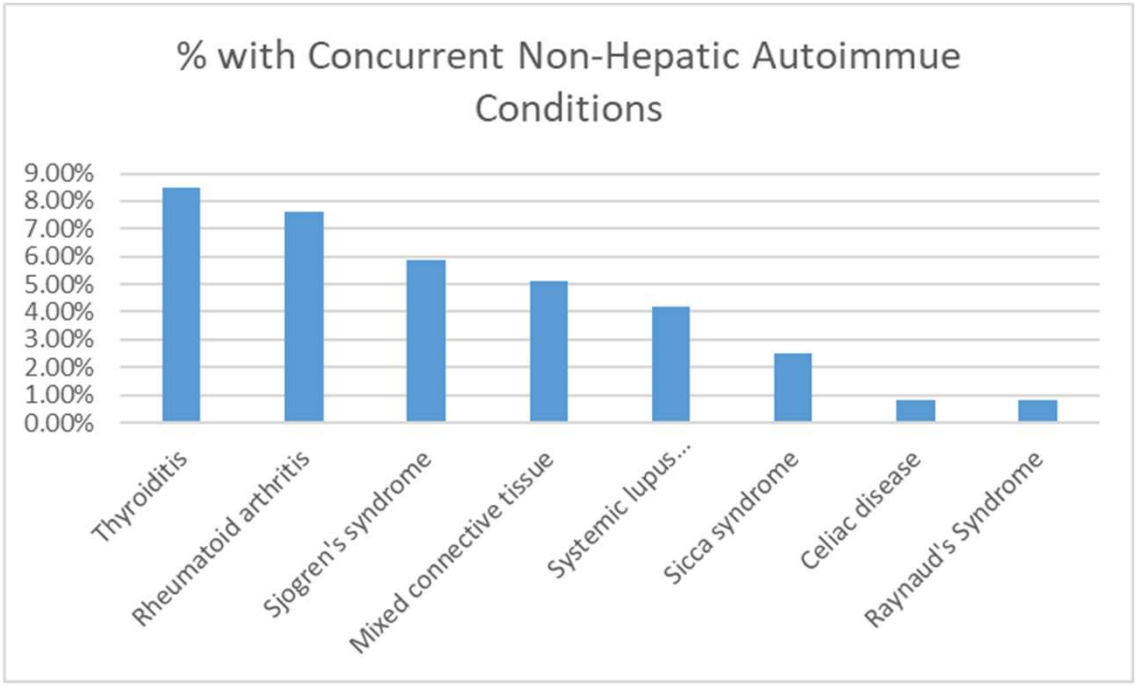


Symptoms at Presentation



>1/3rd have acute hepatitis with jaundice at presentation

Concurrent Autoimmune Diseases are common



Any concurrent non-hepatic autoimmune disease: 29.7%

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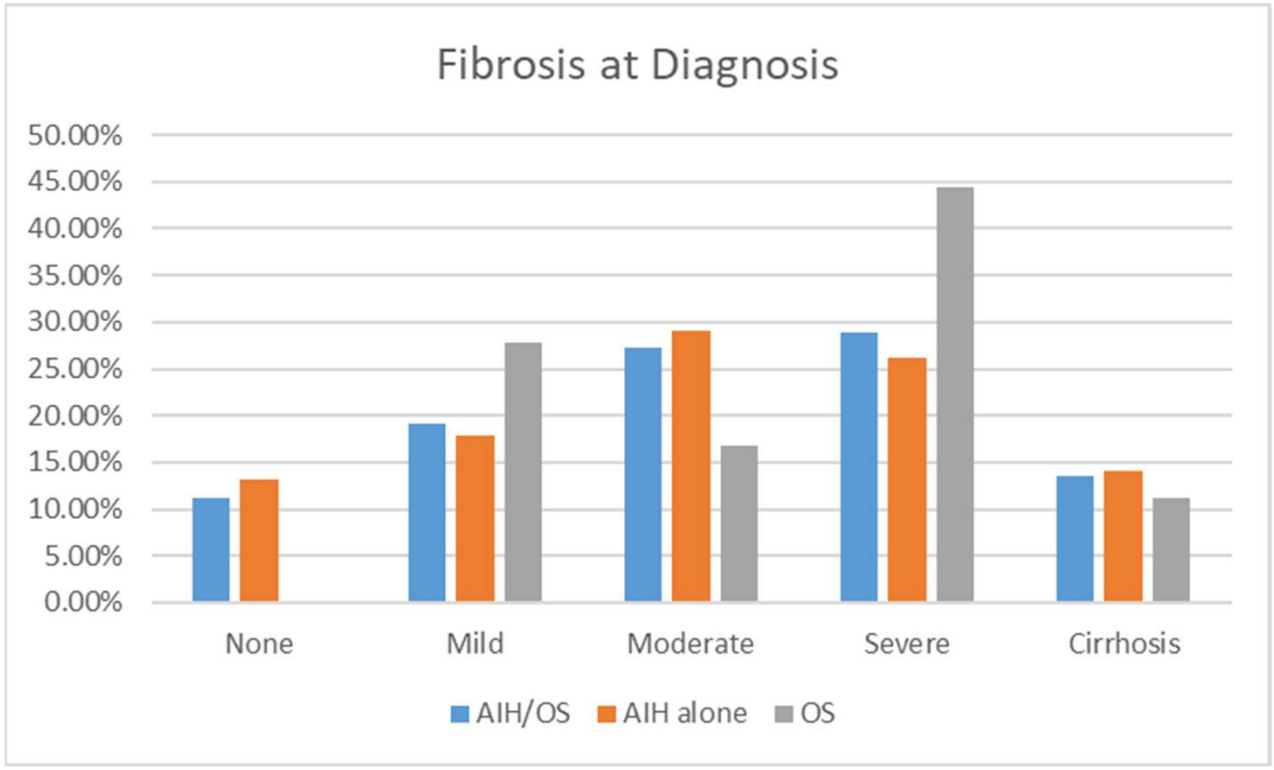
Fibrosis at Diagnosis: 75% have moderate or greater Fibrosis on Biopsy or FibroScan at Diagnosis



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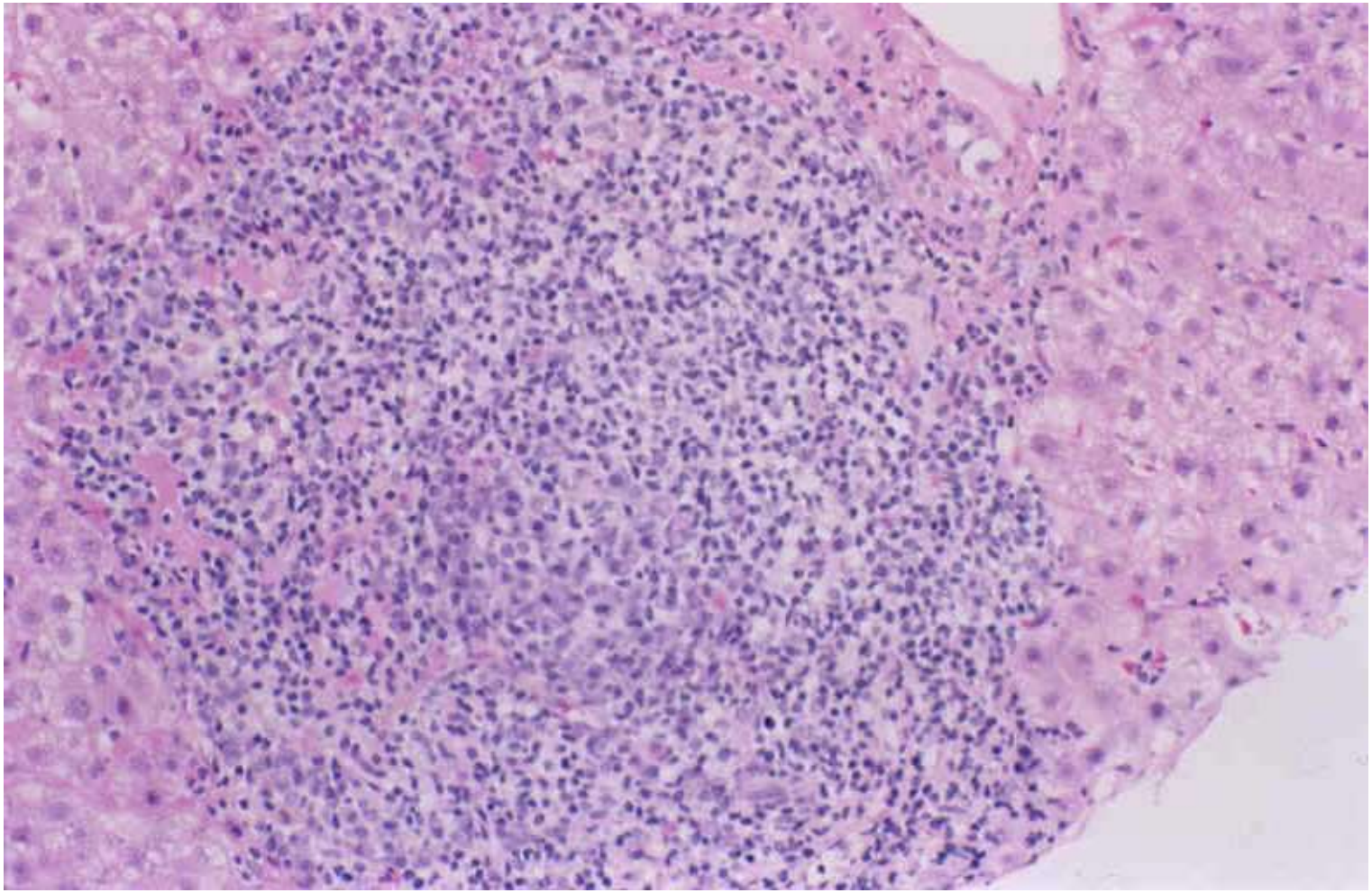
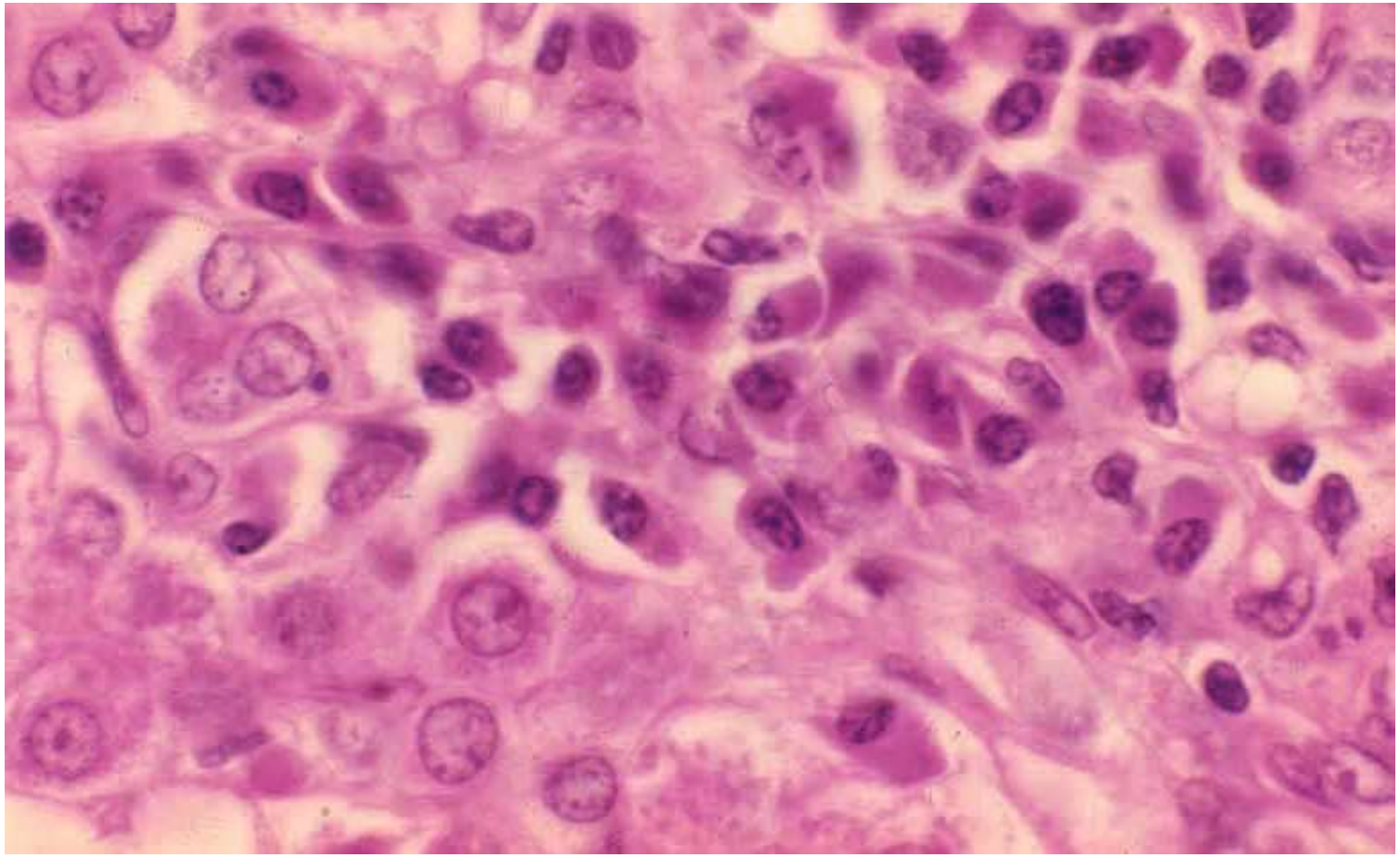
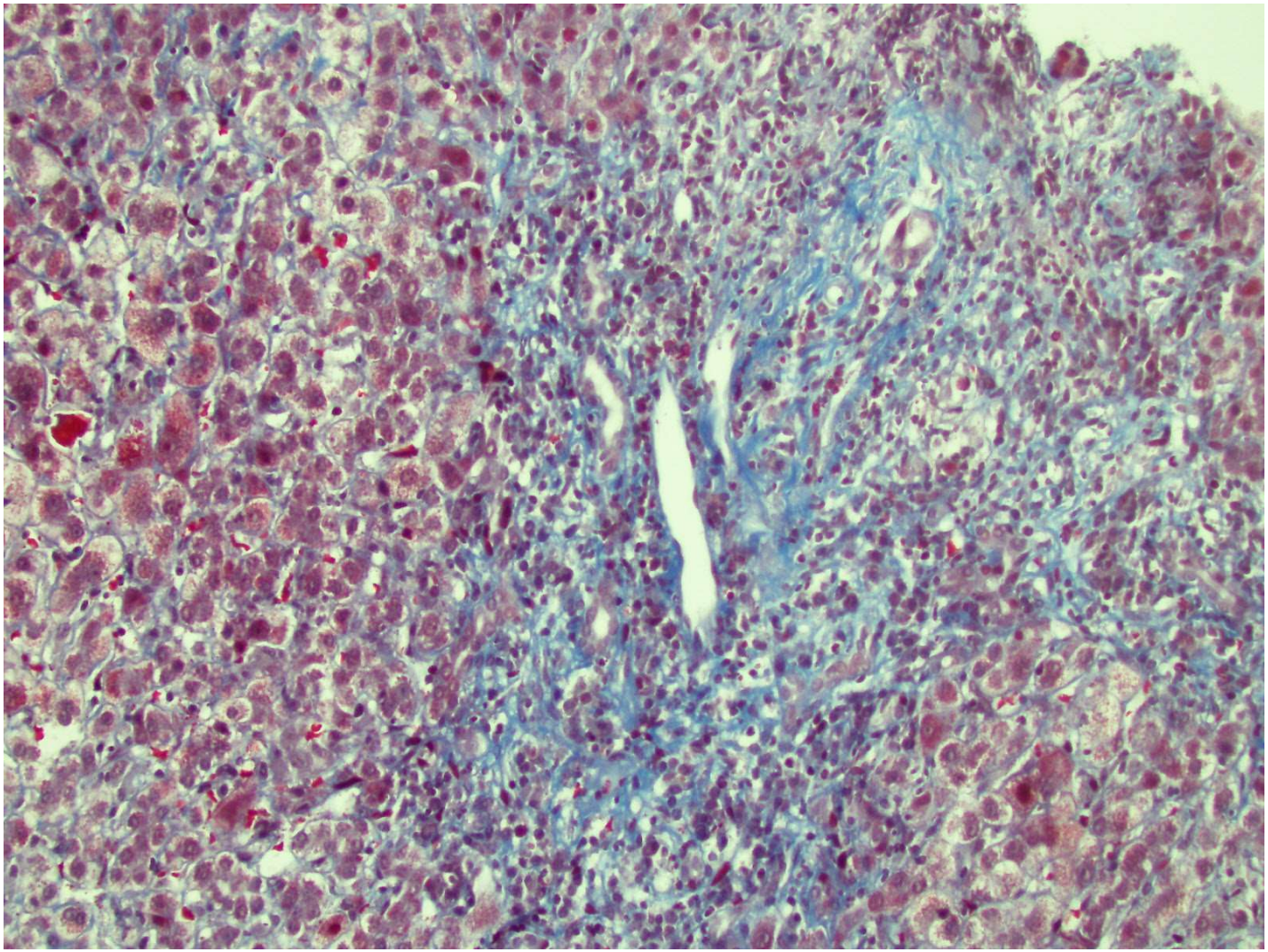
AIH Pathology



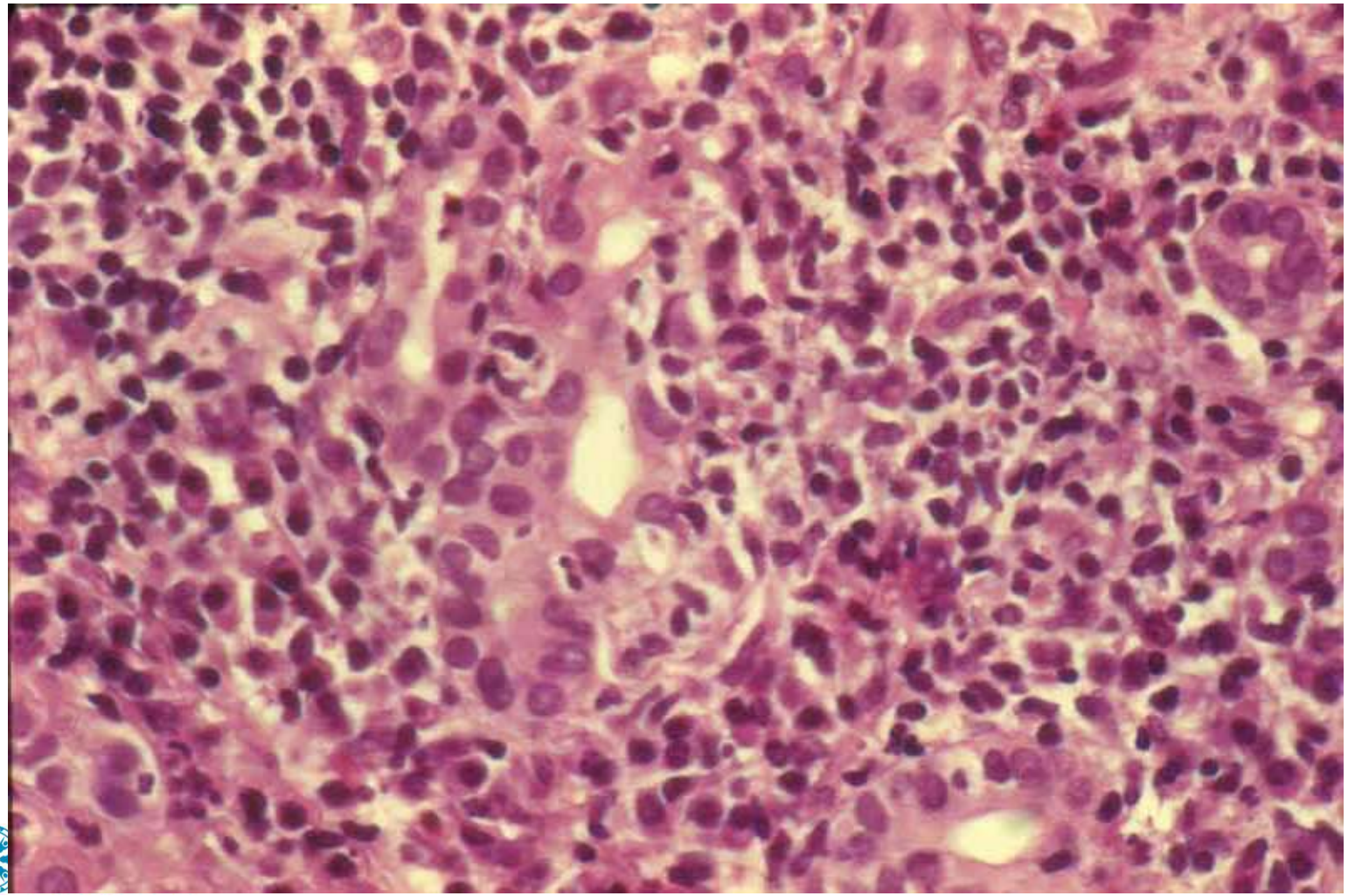
AIH: Plasma Cells



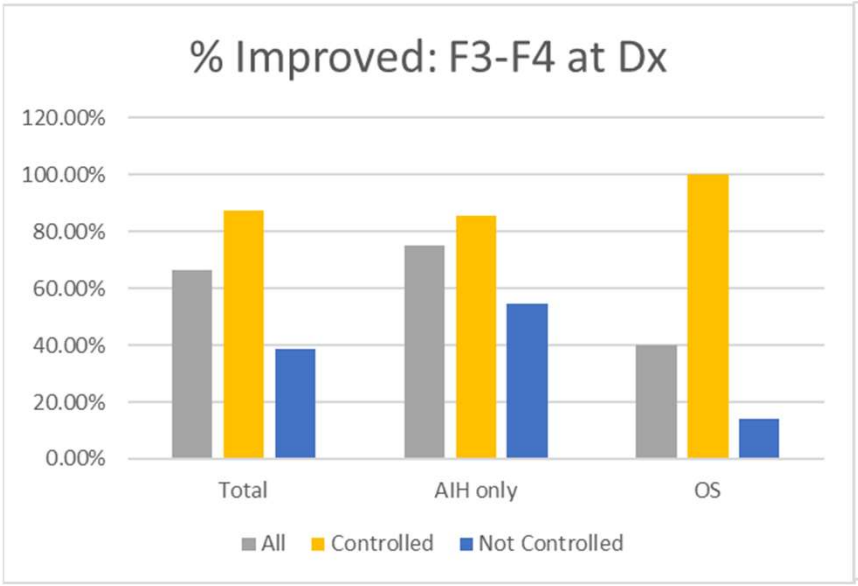
Liver Fibrosis secondary to AIH

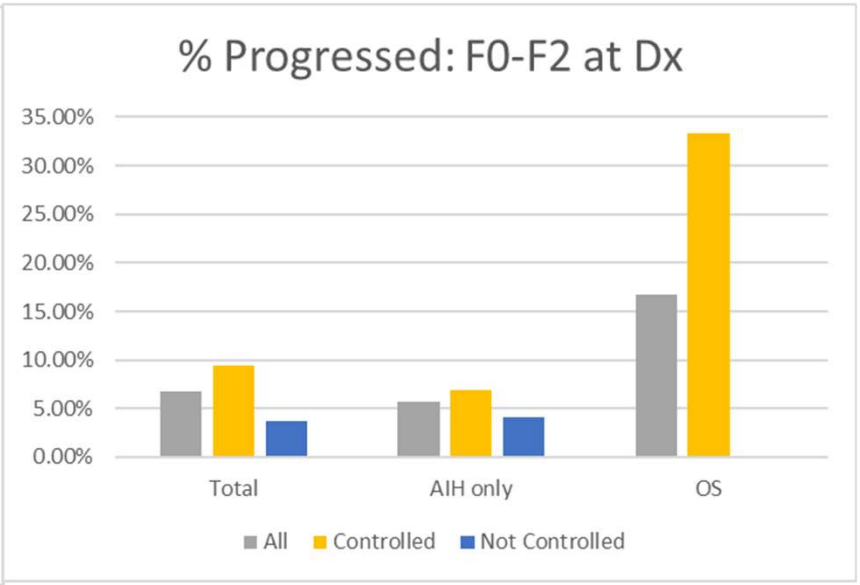


PBC: Florid Bile Duct Lesion: Persons with OS can have features of both AIH and PBC



Fibrosis Improvement/Progression





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Autoimmune Hepatitis Types

- Type 1: 60-70%
  - Anti-Smooth Muscle (Actin) Antibody (ASMA) and/or Anti-Nuclear Antibody (ANA) positive
- Type 2: 4%-20%
  - Anti Liver/Kidney Microsomal (Anti-LKM) Antibody positive:
  - Younger females, frequent in Mediterranean area
  - Occasionally associated with HCV
- Type 3: 10%-30%. Is a variant of Type 1
  - Anti-SLA (Soluble Liver Antigen); variant of type 1
  - Elevated IgG may be only positive lab test

Autoimmune Hepatitis Diagnosis

- Laboratory
  - ANA ≥ 1:40
  - ASMA ≥ 1:40 or Actin > 30 (20-30 intermediate)
  - Anti-LKM if ANA, ASMA negative: antibody to short linear sequence CYP2D6
  - Elevated globulin, gamma globulin or IgG
  - Genetic: HLA B8-DR3 or DR4

Other Autoimmune Antibodies

- Anti-SLA: sole marker in 14% to 20% of AIH
  - Associated with severe disease and with relapse after medication withdrawal
- pANCA: 50%-92%
- Anti-LKM mostly found in type 2 AIH, more frequently in children

AIH in Alaska Natives: Unique Autoantibodies and HLA Associations

- Compared to other populations AN with AIH
  - Higher prevalence of
    - Antibodies to double stranded DNA (47.9%)
    - Anti-neutrophil cytoplasmic antibodies (38%)
  - Lower prevalence of
    - Anti-Ro antibodies (15.5%)
    - Anti-SLA (only one person):
    - No association between anti-Ro and anti-SLA
  - A positive association was found between:
    - HLA DR3 and anti-double stranded DNA
    - HLA DR14 and anti-cytoplasmic antibodies
  - No association between autoantibodies and clinical outcome

Ferucci et al. Liver International 2013

HLA and Antibody Associations in AN Persons with AIH

- At least one allele of HLA DR4 was found in 80% of AN persons with AIH
- 14 of 71 patients in this study had a concurrent rheumatic diagnosis
- The presence of HLA DR4 and absence of HLA DR3 was significantly found in more AN persons with AIH who had a concurrent rheumatic disease
  - Neutropenia was more common in persons with concurrent rheumatic disease while not on meds

Ferucci ED et al. Liver International 2013: ISSN 1478-3223

AIH in Pregnancy

Key Takeaways

- AIH is associated with an increased risk of gestational diabetes, premature births, small for gestational age, and low birth weight babies.
- Pregnant women should be monitored closely before, during, and after pregnancy.
- Flares are most prevalent postpartum.

Outcome	Prevalence Rate	95% CI	No of studies	Cases/Total
Maternal death within pregnancy	2%	1-6%	N=8	3/446
Maternal death Post-partum to within 12 months	3%	2-7%	N=12	3/446
Index presentation AIH	19%	7-42%	N=10	30/305
Pregnancy Flare	13%	8-22%	N=7	28/252
Post-Partum Flare	41%	28-54%	N=10	109/305
Decompensated Cirrhosis (pregnancy or PP)	11%	6-18%	N=8	11/131
Liver transplant @ Baseline	8%	5-13%	N=8	13/255
Neonatal death to within 6 months	3%	2-6%	N=9	8/494
Miscarriage	24%	14-36%	N=6	79/314
Premature birth	14%	10-20%	N=8	65/468
Congenital defect	4%	3-7%	N=7	19/485
Stillbirth	2%	1-3%	N=6	5/443

Outcome	OR

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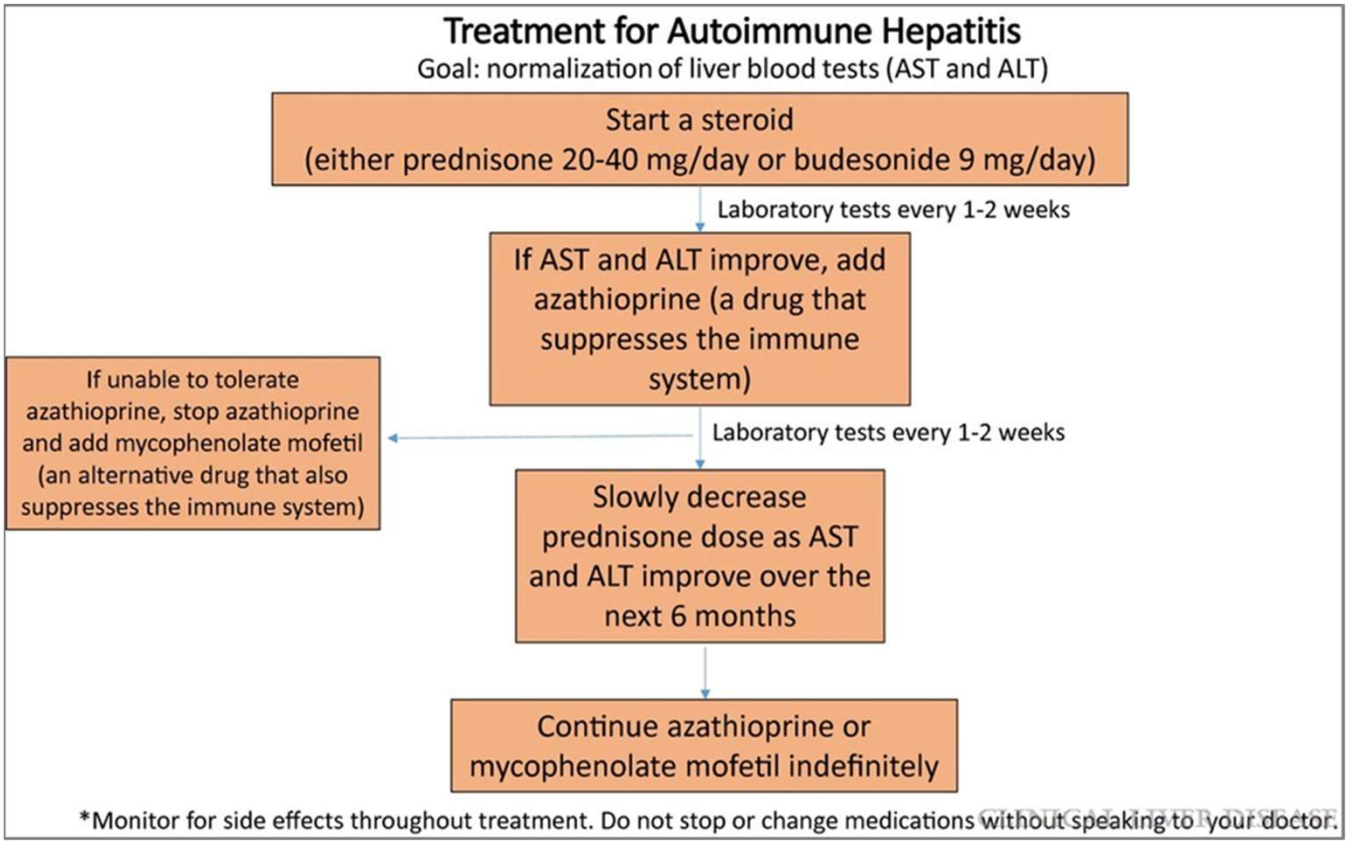
Autoimmune Hepatitis in Pregnancy

- Associated with low birth weight and other complications
  - Close monitoring is crucial
  - Relapse most common postpartum
- Azathioprine: No increased risk in pregnancy, small amounts found in breast milk
- Mycophenolate (MMF): Contraindicated in pregnancy
  - Increased risk of 1st-trimester pregnancy loss and birth defects
- Counsel patients about risks in pregnancy and if they plan to get pregnant, adjust medications appropriately and monitor

FibroScan in AIH

- May be useful to follow patients with cirrhosis as increasing values may predict portal hypertension, risk of esophageal variceal bleed and risk of liver failure
- May be also useful to follow improvements or worsening of fibrosis over time
- One caveat is when LFTs are elevated, FibroScan score will be higher with liver inflammation
- Best to wait a few months after remission to perform FibroScan testing, then every 2-3 years thereafter to determine if fibrosis is improving or progressing
  - Also useful for detecting steatosis and MASLD

Treatment for AIH



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Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: A Patient-Friendly Summary of the 2019 AASLD Guidelines

L. Volk, Michael; Reau, Nancy. Clinical Liver Disease17(2):85-89, February 2021. doi: 10.1002/cld.1080

Thiopurine S-Methyltransferase (TPMT)

- Azathioprine is converted to 6-MP in liver
- 6-MP is converted to 6-TGN by hypoxanthine phosphoribosyl transferase and 6-MMP by TPMT Tyrosine Phosphate Methyl Transferase
- TPMT genotype in Caucasians
  - Homozygous normal 89%
  - Heterozygous 11%
  - Homozygous recessive 0.3%
- TPMT genotype in Alaska Native Population is similar
  - Always measure TPMT in AIH before starting azathioprine

Investigational Findings: Neutropenia in AIH in AN People

- Abnormalities found in the enzyme that metabolizes azathioprine: Thiopurine methyl-transferase (TPMT)
  - 19.3% (1in 5) AN persons with AIH had heterozygous abnormality: 1*/3A compared to one in eight persons in other populations
- However, neutropenia was still common in persons with normal TPMT genotype or enzyme activity

Ferucci ED et al Can J Gastrenterol 1011;25:21-27

AIH TREATMENT

- Initial induction therapy based on 3 randomized controlled trials in early 1970s
  - Prednisone 20-40 mg/day, budesonide 9mg/day or methyl prednisolone 16-32 mg/day. Improvement within 2 weeks expected; Taper rapidly: Goal ALT normalization
  - Azathioprine after checking TPMT, start 25mg, increase to 50mg/day then increase to 1.5 to 2.0 mg/kg/day if tolerated
  - Check Labs LFTS and CBC with Diff every 2 weeks or after changing dosage

- Maintenance Therapy
  - Azathioprine (AZA) 1-2 mg/kg/day with or without prednisone 4-6mg/day. Both may be needed
  - Or prednisone 10-12.5 mg/day
  - Mycophenolate or Tacrolimus as alternative drugs
  - Do not use Azathioprine, Mycophenolate or Tacrolimus in decompensated cirrhosis

AIH treatment and control in AN Population

- Controlled AIH at most recent lab test:
  - AIH alone: 61.5%
  - OS: 45.0%
  - AIH/OS: 59.2%
- Medications:
  - Majority of patients (85.9%) were prescribed either prednisone and azathioprine or methylprednisolone and azathioprine at least once.
  - Persons with features of primary biliary cholangitis or autoimmune cholangitis were given Ursodiol.

Medication intolerance

- Medication intolerance was common:
  - Azathioprine: 69 (AIH: 57; OS: 12)
  - Tacrolimus: 14 (AIH: 13;OS: 1)
  - Mycophenolate motefil: 11 (all AIH)

Tests for Monitoring AIH after Remission

- LFT's every 3 to 4 months
- If on Azathioprine or Mycophenolate, CBC with diff every 3 months
- If on Tacrolimus, Creatinine and GFR plus Tacrolimus levels every 3 months
- IgG yearly
- FibroScan every 2-3 years
- Baseline DEXA then every 2-3 years

Biochemical Remission

- Normal ALT:
  - ≤ 25 IU for women
  - ≤ 35 IU for men
- Normal IgG: may take up to 1-year post normalization of ALT
- Maintained for at least one year

Biochemical Remission

- Majority of AIH/OS patients (62.7%) achieved biochemical remission at some time following diagnosis and treatment
  - AIH: 65.0%
  - OS: 55.0%
- AIH patients less likely to achieve remission:
  - AIH and MASLD: OR 0.31 (95% CI: 0.14-0.70)
  - High Actin at time of diagnosis: OR 0.35 (95% CI=0.15-0.80)

Factors affecting Remission

AIH/OS patient population	Proportion Achieving Remission		Time in years from Diagnosis to Remission: Median (IQR)	OR (95% CI) for Remission
All	62.7%		1.9 (0.5-5.0)	
With Fatty Liver	50.8%	p=0.011	0.6 (0.2 – 1.8)	0.4 (0.2-0.8)
Without Fatty Liver	71.6%		3.3 (1.0 – 6.2)	
With high Actin	56.6%	p=0.008	1.1 (0.3 - 4.1)	0.3 (0.1-0.8)
Without high Actin	79.1%		3.6 (0.2 - 8.7)	

Autoimmune Hepatitis Features

- >90% respond to treatment; Corticosteroids with or without azathioprine
- Spontaneous remissions can occur
- Relapse >70% in patients off medications or if corticosteroids tapered too rapidly (common mistake we have made)

Our Role in Management

- AIH RNs track patients with lab downloads, work with Hepatology provider and PCP to taper/titrate medications
- Hepatology Dept sends letters reminding patients to get blood draws every 3-4 months if in remission; sends list of patients needing testing to primary care providers to order tests
  - LFTs
  - CBC with differential if on azathioprine or mycophenolate
  - Tacrolimus trough level and creatinine if on Tacrolimus
- Hepatitis clinic visits depends on control
  - Every 6-12 months if in remission: yearly in field clinics

Five and Ten Year Survival

- Five-year survival:
  - AIH alone: 99.2% (95% CI = 99.5%-99.9%)
  - OS: 100.0% (95% CI: 83.9%-100.0%)
  - Combined: 99.3% (95% CI: 96.1%-99.9%)
- Ten-year survival:
  - AIH alone: 95.9% (95% CI: 90.8%-98.2%)
  - OS: 85.0% (95% CI: 64.0%-94.8%)
  - Combined: 94.4% (95% CI: 89.3%-97.1%)

Summary

- AIH is a rare disease, but much more common in AN population
  - May co-exist with features of NAFLD or heavy alcohol usage
  - May overlap with Primary Biliary Cholangitis
  - May progress to cirrhosis, liver transplant, HCC, or liver related-death if untreated but controlling this disease can result in long-term survival, regression of fibrosis
- Can be controlled with treatment
  - Time to remission varies
  - Relapse may occur if off meds or disease not adequately suppressed on meds
  - Side effects to current treatment are common requiring careful follow-up (LFTs, CBC every 3-months and FibroScan every 1-3 years)
  - Most but not everyone responds to treatment
  - Biggest challenge is with patients who go on and off their medications

Quiz: Select the Best Answer

1. AIH has a bad outcome, even on treatment most persons will expire in 5-10 years
2. AIH only occurs after age 30
3. Women have a slightly higher prevalence of AIH
4. Remission can occur in up to 90% of persons
5. Liver biopsy is not helpful in AIH diagnosis

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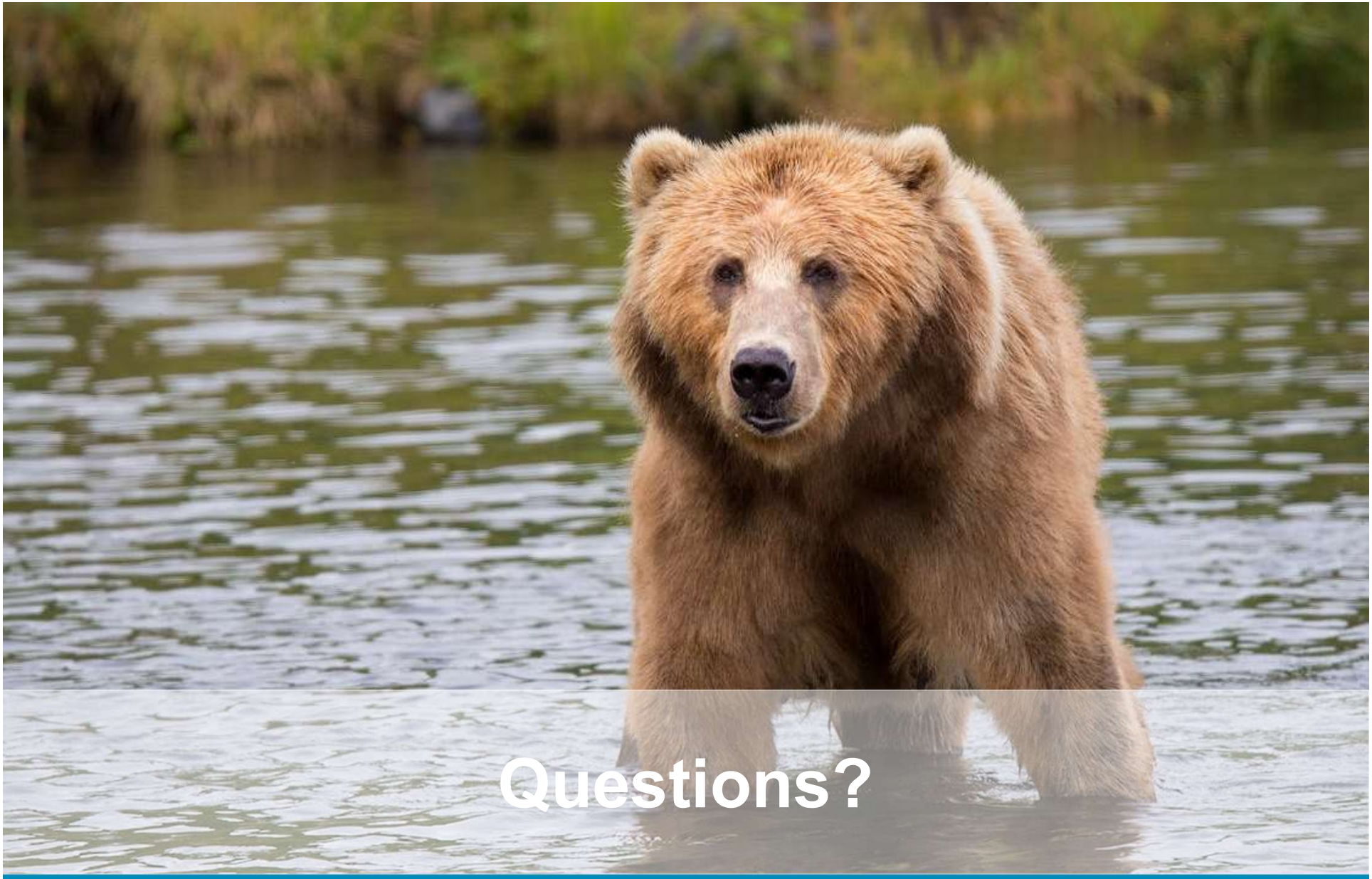
2. AIH only occurs after age 30
3. Women have a slightly higher prevalence of AIH
4. Remission can occur in up to 90% of persons
   Correct Answer
5. Liver biopsy is not helpful in AIH diagnosis



Questions?

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Case Presentation

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AK Liver Disease ECHO

- Third Thursday of every month from noon-1:00 PM AKST
- 1CE/CME offered per session
- www.anthc.org/AK-LD-ECHO
- 2023 Theme: Ways You Can Reduce Morbidity and Mortality From Liver Disease
  - October 19: Stressing the Importance of Exercise as NAFLD Treatment Now that it is Getting Dark and Cold

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Additional learning opportunities

- AK ID ECHO: HCV, HIV, PrEP, STIs
  - Second Tuesday of every month from noon-1:00 PM AKST
    - 1CE/CME offered per session
  - anthc.org/ak-id-echo
  - October 10: DoxyPEP presented by Andrew Yu, RN, IHS
- LiverConnect Webinar Program
  - Second Tuesday of every month 8:00-9:00 AM AKST
    - 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

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