WELCOME TO
AK LIVER DISEASE ECHO

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

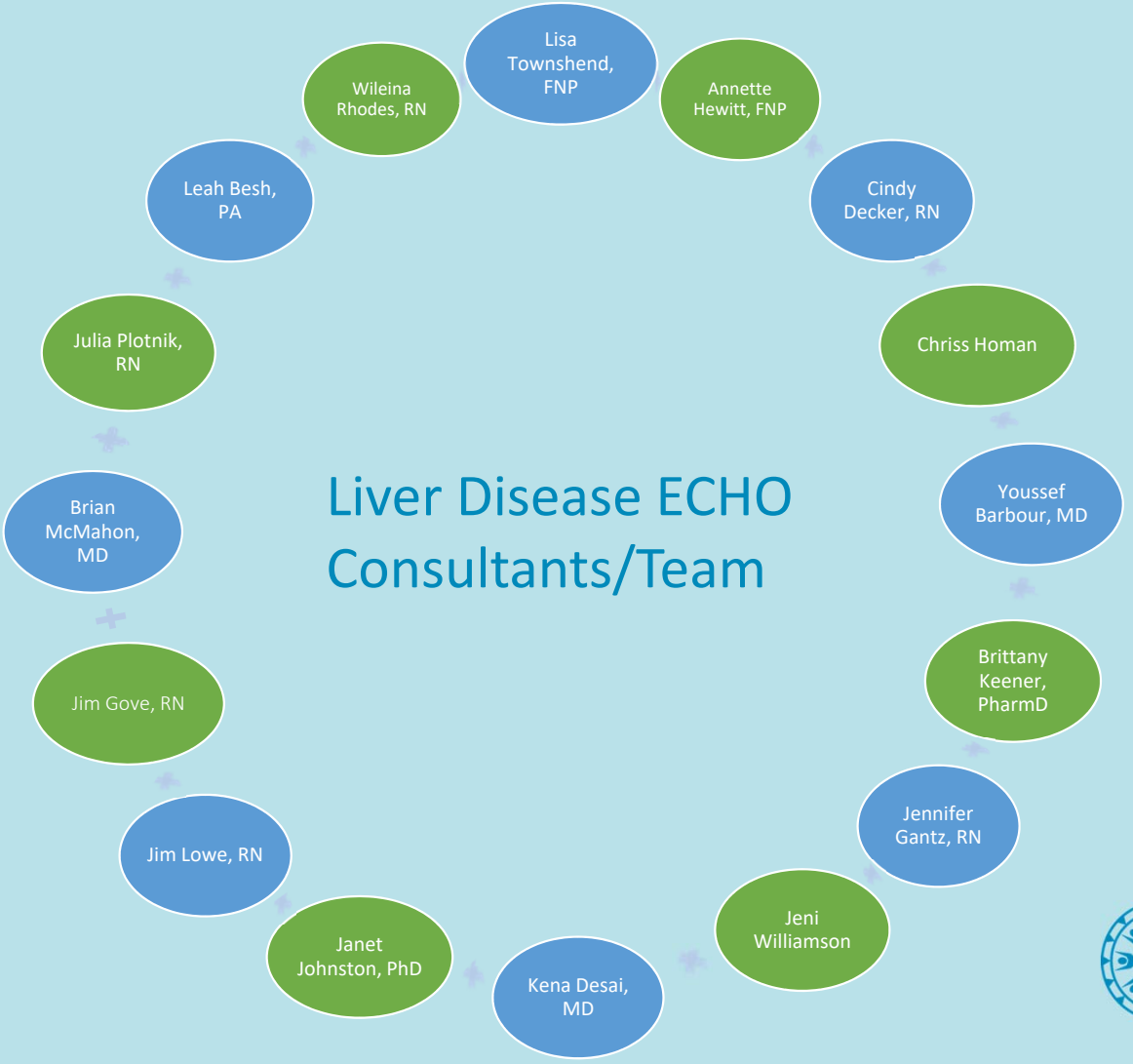
NPAIHB
Indian Leadership for Indian Health

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

Liver Disease ECHO Consultants/Team



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Welcome to AK Liver Disease ECHO

Approved Provider Statements:

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.

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ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

Addressing Safe Medication Prescribing

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Alaska Liver Disease ECHO
May 18, 2023

Conflict of Interest

- I have no conflict of interest to disclose

Test Your Knowledge

- All medications are safe to use in liver disease
  - True or False
- Pharmacokinetic and pharmacodynamic changes are the only factors to consider when prescribing medications in liver disease
  - True or False
- Studies have shown 90% of adverse drug events are preventable due to excessively high doses or contraindications
  - True or False

Objectives

- Review medication safety basics
- Review risk of adverse drug events in liver disease
- Review pathophysiological abnormalities that can occur in patients with cirrhosis and the consequences on pharmacokinetic parameters
- Review prescribing recommendations

Medication Safety

- Each year in the US, adverse drug events (ADEs) cause approximately 1.3 million visits to emergency departments & 350,000 hospitalizations
- 82% of US adults take at least one medication
- 29% of US adults take five or more medications
- $3.5 billion is spent on excess medical costs of ADEs annually
- More than 40% of costs related to ambulatory ADEs may be preventable
- ADEs are likely to grow:
  - New medications
  - New uses for older medications
  - Aging population
  - Increased use
  - Expanded insurance coverage/access to care

Medication Risks in Liver Disease

- Prone to develop ADEs due to changes in pharmacokinetics and pharmacodynamics
  - Can result in increased plasma drug concentrations
  - Altered hepatic blood flow
  - Reduced drug-binding proteins
  - Severity of liver dysfunction
- Nearly 30% of those with liver cirrhosis experience ADEs
  - May have increased susceptibility to toxicological effects of medications due to pathophysiological changes
- 20% of medications in patients with liver cirrhosis are dosed incorrectly
- In studies, 78% of ADEs are preventable due to excessively high doses or contraindications

Factors Influencing Health Behaviors in Liver Disease

- Available evidence supports multifaceted, collaborative, and multidisciplinary models of care to improve outcomes

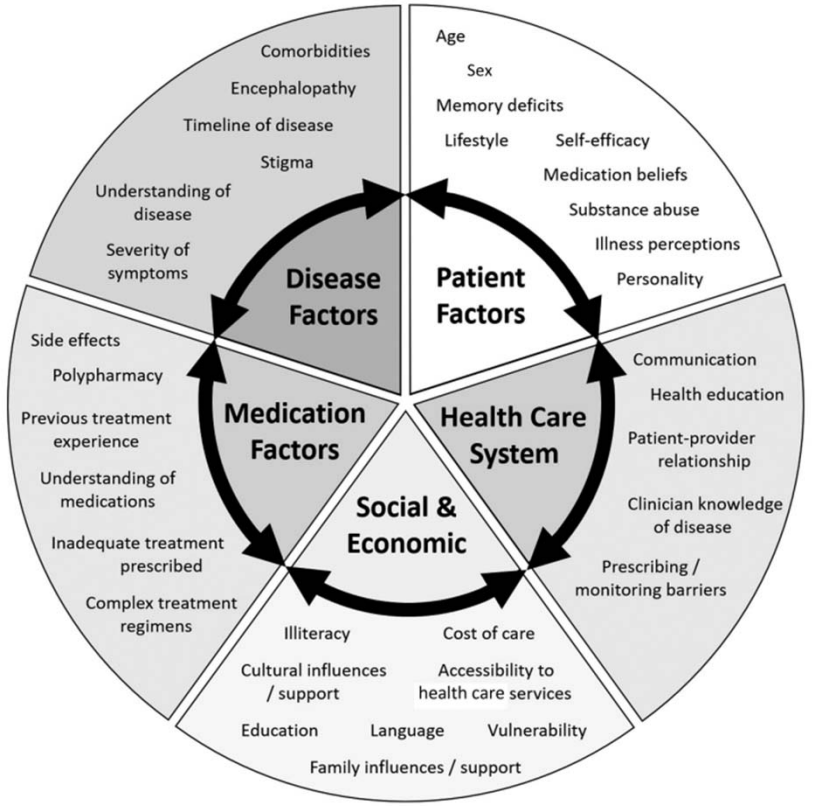

FIG. 1. Factors that may influence health behaviors in people with CLD.

Pathophysiological and Pharmacokinetic Changes

	Pathophysiological change	Pharmacokinetic change
Absorption	• Portal hypertensive gastropathy, ulcers of the upper gastrointestinal tract, gastritis • Increased intestinal permeability • Impaired gastrointestinal motility with delayed gastric emptying	• Altered extent of drug absorption • Decreased rate of absorption
	• Altered hepatic blood flow (e.g. portosystemic shunts, TIPS) • Reduced intrinsic clearance	• Decreased first-pass effect resulting in a higher bioavailability • Pro-drug metabolism diminished
Distribution	• Decreased levels of plasma proteins (e.g. albumin, α_1-acid glycoprotein) due to impaired synthesis in the liver • Accumulation of endogenous substances, such as bilirubin, displacing binding sites of plasma proteins • Fluid retention (ascites, edema)	• Reduced plasma protein binding resulting in a larger fraction of unbound drug • Enlarged volume of distribution
Metabolism	• Alterations in hepatic architecture including hepatocellular necrosis, altered blood flow, and nodular formation	• Reduced activity or expression of phase I and II drug-metabolizing enzymes (reduced intrinsic clearance). The extent of reduced activity differs per enzyme. Some enzymes are very sensitive for these pathophysiological changes (e.g. CYP2C19), while others are affected in a later stage (e.g. CYP2D6). • Changes in stereoselectivity of hepatic drug metabolism
	• Reduced blood flow across the liver	• Delayed clearance by drug-metabolizing enzymes
Elimination	• Bile flow obstruction, due to cancer or sclerosing cholangitis • Reduced protein transporter expression	• Biliary excretion reduced • Disrupted enterohepatic recycling
	• In advanced cirrhosis, renal impairment	• Reduced renal elimination

TIPS: transjugular intrahepatic portosystemic shunt

Pharmacokinetic Changes

- Changes in CYP450 activity may occur
  - Typically reduced, resulting in decreased drug clearance and increased serum drug concentrations
  - 1A2 and 3A4 have at least 50% reduction in activity in cirrhosis
  - 2C, 2A, and 2B are mostly unaltered
  - Medications with a low extraction ratio (warfarin, phenytoin, carbamazepine, lorazepam) rely heavily on clearance through CYP450 enzymes and will be impacted more significantly
- Albumin production is reduced by 60 to 80% in cirrhosis
  - Medications with high protein-binding to albumin become unbound increasing the risk of toxicity
  - Dose reductions may be needed for highly protein-bound medications (warfarin, phenytoin, diazepam, fluoxetine, digoxin, valproic acid)

Toxicological Effects in Cirrhosis

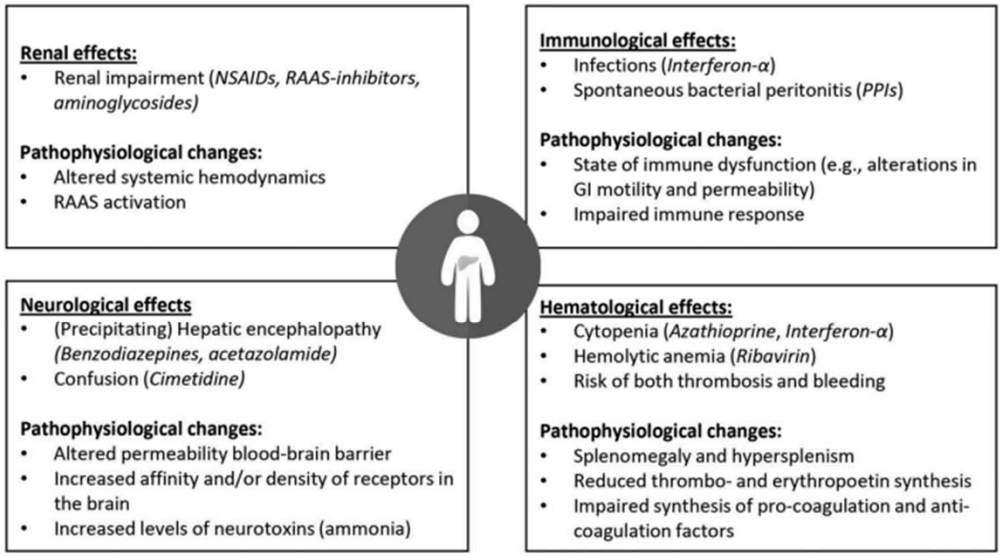

Figure 1. Overview of toxicological effects that patients with cirrhosis seem to be more susceptible to compared to healthy controls and underlying pathophysiological changes.

ADR: adverse drug reaction, GI: gastro-intestinal, PPIs: proton pump inhibitors, NSAIDS: non-steroidal anti-inflammatory drugs, RAAS: renin-angiotensin-aldosterone system

Optimizing Medications

- On average, patients with cirrhosis are prescribed 3 to 10 medications
- Optimize medications to prevent drug-drug interactions, ADEs, and toxicity
- Review indications and need for medications
- Complete med history & reconciliation including OTC and herbal products
- Consider severity of cirrhosis

Summary of Drug Adjustments in Cirrhosis

Therapeutic Category	Safe	Avoid
Acid-suppressing agents	Esomeprazole[a] Famotidine	Lansoprazole Omeprazole[a] Pantoprazole Rabeprazole Cimetidine
Analgesics		Acetaminophen[a] COX-2 inhibitors[a] NSAIDs
Antibiotics	Amoxicillin Amoxicillin/ clavulanic acid Ciprofloxacin Rifaximin	Azithromycin Erythromycin
Antidiabetic drugs	Insulin Glucagon-like peptide-1 agonists Sulfonylureas[a] Dipeptidyl peptidase-4 SGLT-2 inhibitors	Metformin Pioglitazone
Antihypertensives	Calcium channel blockers[a]	ACE inhibitors ARBs Verapamil[a]
Diuretics	Furosemide Spironolactone Hydrochlorothiazide	
Lipid-lowering agents	Cholestyramine	Statins[a]

[a] *Dose adjustment necessary.*
ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker; COX: cyclooxygenase; NSAID: nonsteroidal anti-inflammatory drug; SGLT-2: sodium-glucose-linked transporter-2.

Approach to Prescribing in Liver Disease

- Should be individualized and pragmatic
- Balance risk vs. benefits
- Cautious approach with regular monitoring
- In general, medications with high bio-availability, minimal hepatic metabolism, low-moderate protein-binding, short half-lives, and no sedative, constipating, or hepatotoxic effects are safer
- Consider dose reduction if the medication normally:
  - Has low systemic bio-availability due to high first-pass metabolism
  - Is highly protein-bound and the patient has hypo-albuminemia and/or elevated plasma bilirubin
  - Is cleared mainly by phase I hepatic metabolism (CYP1A2, 2C19, 2D6, or 3A4) and has a narrow therapeutic range or a long half-life

Approach to Prescribing in Liver Disease

- Factors indicative of severe hepatic impairment and possible need for dose reduction:
  - PT >130% of normal
  - Platelets $<150 \times 10^9$/L
  - Bilirubin >5.8mg/dL
  - Severe cirrhosis (Child-Pugh C)
  - Ascites
  - Hepatic encephalopathy
  - Hyponatremia
  - Moderate renal impairment (eGFR <60mL/min/1.73m^2)

Approach to Prescribing in Liver Disease

- Systematic literature review combined with expert opinion from a panel of 10 experts:
  - Classified each medication as safe, no additional risk known, additional risks known, unsafe, unknown or the safety class was dependent on the severity of liver cirrhosis
  - Formulated 218 recommendations for 209 medications
  - Safe 13.8%, no additional risks known 27.5%, additional risks known 1.4%, unsafe 13.8%; in 26.1% of the recommendations safety depended on the severity of liver cirrhosis and was unknown for 17.9%, in 31% a dose adjustment was needed

Table 3 Overview of drug use per safety class and the five most frequently used drugs per class according to Weersink et al. [11]

Safety class[a]	Drug	ATC code	No. of users	Period prevalence during total follow-up (%)
Safe	Total ($n=27$)[b]		4836	86.1
	Spironolactone	C03DA01	2734	48.7
	Furosemide	C03CA01	2470	44.0
	Lactulose	A06AD11	1661	29.6
	Amoxicillin and enzyme inhibitor	J01CR02	1416	25.2
	Propranolol	C07AA05	1354	24.1
No additional risks known	Total ($n=50$)[b]		4366	77.7
	Macrogol, combinations	A06AD65	1623	28.9
	Tramadol	N02AX02	1091	19.4
	Esomeprazole	A02BC05	924	16.4
	Acetylsalicylic acid	B01AC06	789	14.0
	Metoclopramide	A03FA01	711	12.7
Additional risks known	Total ($n=3$)[b,c]		156	2.8
	Azathioprine	L04AX01	99	1.8
	Methadone	N07BC02	52	0.9
	Heparin	B01AB01	6	0.1
Unsafe	Total ($n=25$)[b]		3368	60.0
	Pantoprazole	A02BC02	1963	34.9
	Diclofenac	M01AB05	1246	22.2
	Ibuprofen	M01AE01	612	10.9
	Naproxen	M01AE02	592	10.5
	Atorvastatin	C10AA05	347	6.2
Unknown	Total ($n=27$)[b]		2244	39.9
	Doxycycline	J01AA02	1080	19.2
	Nitrofurantoin	J01XE01	622	11.1
	Flucloxacillin	J01CF05	619	11.0
	Magnesium hydroxide	A02AA04	240	4.3
	Pheneticillin	J01CE05	160	2.8
Depending on the severity of cirrhosis[d]	Total ($n=49$)[b]		3872	68.9
	Omeprazole	A02BC01	1809	32.2
	Codeine	R05DA04	908	16.2
	Metoprolol	C07AB02	872	15.5
	Simvastatin	C10AA01	846	15.1
	Fentanyl	N02AB03 N01AH01	594	10.6
Safety not yet evaluated	Total ($n=1005$)[e]		5415	96.4
	Thiamine (vitamin B1)	A11DA01	1374	24.5
	Temazepam	N05CD07	1302	23.2
	Other emollients and protectives	D02AX	1236	22.0
	Oxazepam	N05BA04	1121	20.0
	Phytomenadione	B02BA01	894	15.9

The total number of users per safety class is calculated for the total follow-up and includes all drugs from that class, not only the top five. Patients were only counted once in the total number

ATC Anatomical Therapeutic Chemical

[a]The drug-risk category indicates potential safety risks

[b]For drugs evaluated by Weersink et al. [11], total numbers represent the number of evaluated drugs prescribed

[c]This is one of the top three because only three drugs were part of this class

[d]Since no data were available about the severity of cirrhosis (Child–Pugh class), these drugs could not be classified further

[e]For drugs with no safety evaluation as yet, the total is the total number of ATC classes without evaluation

Approach to Prescribing in Liver Disease

- Retrospective cohort study based in the Netherlands
- 5618 patients were included and followed for a median of 3 years and compared to previously developed safety recommendations for 209 medications
- Median of 9 medications were used per patient
  - Proton pump inhibitors (53.9%)
  - Aldosterone antagonists (43.6%)
  - Sulfonamide diuretics (41.3%)
- 48.3% of >100K prescriptions consisted of medications with a safety recommendation
- During the total follow-up, the prevalence of potentially unsafe medication use was 60%

Summary

- Patients with cirrhosis have an increased risk of ADEs due to pharmacokinetic and pharmacodynamic changes, and the large number of medications they use
- Potentially unsafe medication use is common in patients with cirrhosis and more efforts are needed to decrease the use of these medications in these patients
- Clinical decision support, multidisciplinary consultations, individualized treatment plans, and close monitoring should all be considered when prescribing medications with liver disease

Test Your Knowledge

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  - True or False
- Pharmacokinetic and pharmacodynamic changes are the only factors to consider when prescribing medications in liver disease
  - True or False
- Studies have shown 90% of adverse drug events are preventable due to excessively high doses or contraindications
  - True or False

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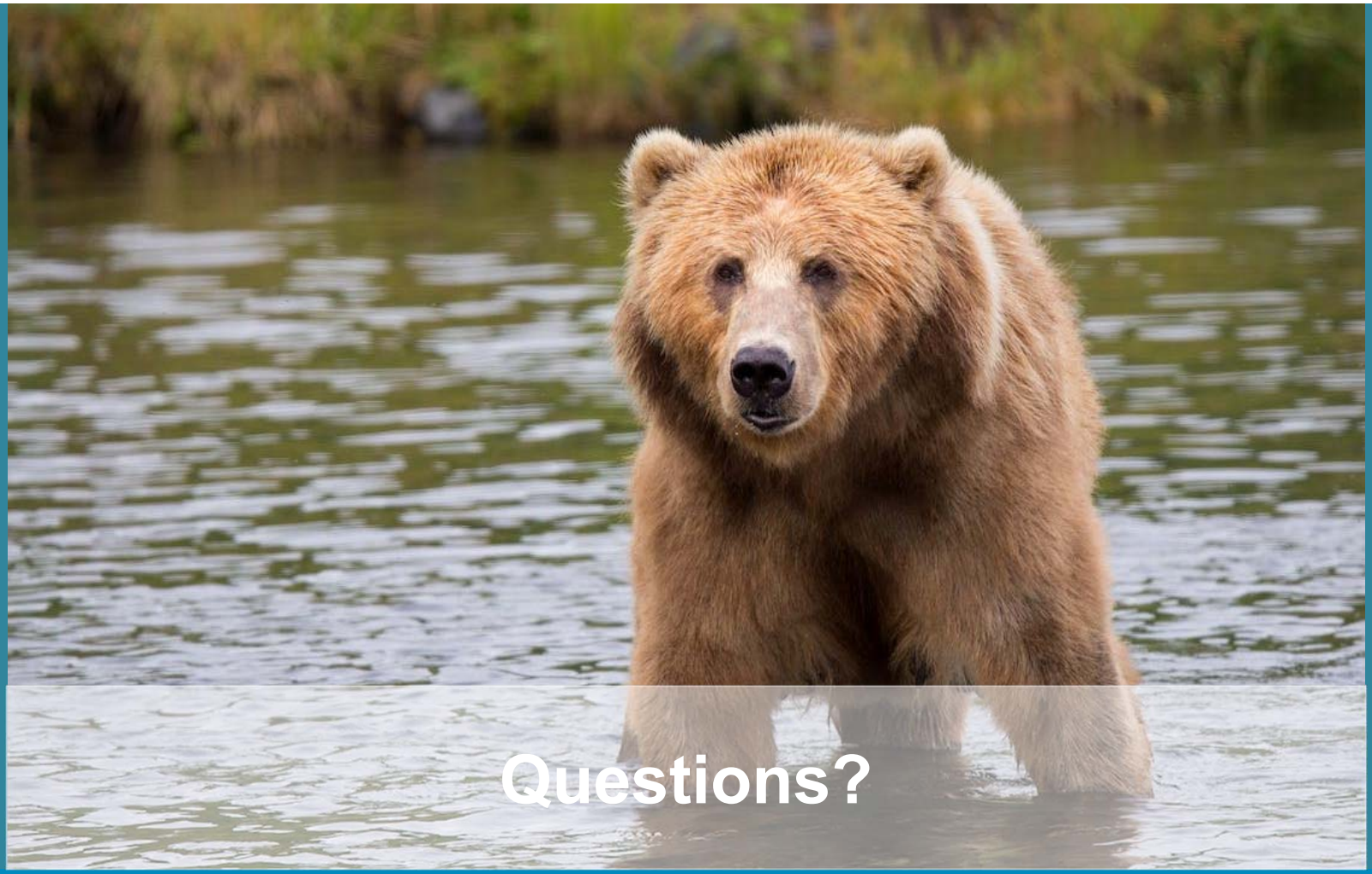

Questions?

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Case Presentation

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AK Liver Disease ECHO

- Second Tuesday of every month from noon-1:00PM AKST
- 1CE/CME offered per session
- anthc.org/project-echo/alaska-liver-disease-echo
- 2023 Theme: Ways You Can Reduce Morbidity and Mortality From Liver Disease
  - June 15: Effective Strategies for Alcohol Use Disorder Screening – When, Where, and How to Implement
  - July 20: Emphasizing Nutrition for Liver Health

Additional learning opportunities

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

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