Primary Biliary Cholangitis

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Disclosure:

YOUSSEF BARBOUR, MD OF THE LIVER DISEASE & HEPATITIS PROGRAM IS PRIMARY INVESTIGATOR ON AN INVESTIGATOR-SPONSORED OBSERVATIONAL STUDY OF ALASKA NATIVE/AMERICAN INDIAN PERSONS RECEIVING SOFOSBUVIR-BASED TREATMENT FOR HEPATITIS C INFECTION. THIS STUDY IS FUNDED IN-PART BY A CONTRACT WITH GILEAD SCIENCES.

Objectives

Following this presentation, the participants will be able to:

- list the differential diagnoses for elevated alkaline phosphatase
- recognize PBC in its early stages
- discuss the pharmacologic treatment for PBC and its complications and understand how to incorporate these medications into patient care
- identify associated morbidities with PBC
- state the incidence of PBC among Alaska Native persons

Pre-Test Question #1

Which is a true statement about Cholestatic Liver Disease?

a. ERCP is the first step in evaluation

b. Alk Phos is always <4 times ULN

c. GGT is abnormal in extra hepatic cholestasis

d. Cholestasis of pregnancy poses no risk on the fetus

Pre-Test Question #2

The following are unique features of PBC except:

a. It is always AMA positive.

b. Portal HTN can occur before cirrhosis.

c. It involves small intra hepatic bile ducts.

d. Bilirubin level is the best predictor of survival.

Pre-Test Question #3

Which is true about PBC among Alaska Natives?

a. Prevalence is among the lowest in the world

b. Prevalence is among the highest in the world

c. Prevalence is comparable to global prevalence

d. It consists mostly of AMA- negative PBC

Case Study 1

- 32 y/o female, from western Alaska presented with chronic symptoms of lethargy and pruritus.
- PMH: HTN, Cholestasis of pregnancy [took Ursodiol for this], RUQ pain for 4yrs [mostly relieved by Cholecystectomy 1 year prior], impaired fasting glucose
- FH: cousin has PBC, Father has RA
- SH: Alcohol: 9 beers 1-2 times a week, sometimes more
- LAB: Alk Phos elevated for 6 years

Case study 1

- Work up:
- Labs: ALT/AST: 138/94, Alp: 343, T.Bili: 0.3, Albumin 4.1, GGT: 366
- Autoimmune markers: ANA: neg, SMA: <20, IgG: 1514, AMA: 1:320 IgM: 352
- Viral hepatitis panel: negative

- Liver Biopsy:
- Decreased bile ducts. Chronic portal inflammation. Mildly increased portal fibrosis, consistent with early PBC

Case study 1

- Treatment:
- Ursodiol 300 mg daily, gradually increased to 900 mg daily

- Follow up:
- ALT/AST normalized in few months.
- Alp: slow improvement, to drop in 1 year from 339 to 95
- Within the first year of treatment, patient got pregnant, Ursodiol continued, itching got worse, Benadryl helped.

Causes of an elevated alkaline phosphatase

Marked elevation (≥4 times the upper limit of normal)*	**Extrahepatic biliary obstruction¶**
	Choledocholithiasis (most common) ▪ Uncomplicated ▪ Complicated (biliary pancreatitis, acute cholangitis)
	Malignant obstruction ▪ Pancreas ▪ Gallbladder ▪ Ampulla of Vater ▪ Bile duct
	Biliary strictures ▪ Primary sclerosing cholangitis with extrahepatic bile duct stricture ▪ Complications after invasive procedures ▪ Chronic pancreatitis with stricturing of distal bile duct ▪ Biliary anastomotic stricture following liver transplantation
	Infections ▪ AIDS cholangiopathy ▪ *Ascaris lumbricoides* ▪ Liver flukes
	Intrahepatic cholestasis
	Drug and toxins associated with cholestasis△
	Primary biliary cirrhosis△
	Primary sclerosing cholangitis△
	Intrahepatic cholestasis of pregnancy
	Benign postoperative cholestasis
	Total parenteral nutrition
	Infiltrative diseases△ ▪ Amyloidosis ▪ Lymphoma ▪ Sarcoidosis ▪ Tuberculosis ▪ Hepatic abscess
	Metastatic carcinoma to the liver△
	Liver allograft rejection
	Ischemic cholangiopathy
	Alcoholic hepatitis
	Sickle cell disease (hepatic crisis)
	Nonhepatic causes◇
	Transient hyperphosphatemia of infancy and childhood
Moderate elevation (<4 times upper limit normal)	**Hepatic causes**
	Nonspecific, seen with all types of liver disease including: ▪ Hepatitis: viral, chronic, alcoholic ▪ Cirrhosis ▪ Infiltrative diseases of the liver ▪ Hypoperfusion states: sepsis, heart failure
	Nonhepatic causes◇
	Physiologic (children and adolescents)
	Third trimester of pregnancy
	Influx of intestinal alkaline phosphatase after eating a fatty meal (individuals with blood type O or B)
	High bone turnover ▪ Growth ▪ Healing fractures ▪ Osteomalacia ▪ Paget disease of bone ▪ Osteogenic sarcoma, bone metastasis ▪ Hyperparathyroidism ▪ Hyperthyroidism
	Extrahepatic disease ▪ Myeloid metaplasia ▪ Peritonitis ▪ Diabetes mellitus ▪ Subacute thyroiditis ▪ Gastric ulcer (uncomplicated) ▪ Extrahepatic tumors • Osteosarcoma • Lung • Gastric • Head and neck • Renal cell • Ovarian • Uterine • Hodgkin lymphoma

* The alkaline phosphatase value may vary and be <4 times the upper limit of normal at times (eg, early in the disease process).
¶ May cause an isolated elevation in hepatic alkaline phosphatase if partial obstruction.
△ May cause an isolated elevation in hepatic alkaline phosphatase.
◇ Alkaline phosphatase may be derived from several sites including the liver, bone, third trimester placenta, intestine, and kidneys. An elevation in alkaline phosphatase with a normal gamma-glutamyl transpeptidase or 5'-nucleotidase suggests a nonhepatic source of alkaline phosphatase.

Primary Biliary Cholangitis (PBC)

- Etiology is thought to be due to a combination of genetic predisposition and environmental triggers.
- Several large epidemiologic studies have been performed and have suggested an association with UTIs, HRT, nail polish, past cigarette smoking, and toxic waste sites.
- One critical and unique feature of PBC is the high degree of specificity for involvement of the small intrahepatic bile ducts

AMA in PBC

- The characteristic serologic hallmark of PBC is the AMA, a highly disease-specific autoantibody found in 90-95% of patients and less than 1% of normal controls
- It is estimated that 0.5% of the general population is AMA-positive, which means that fewer than 10% of patients with AMA will develop PBC
- The presence or absence of antibody, rather than the magnitude of antibody, is most important.

PBC diagnosis

- Elevated Alp>> check GGT; if positive
- Exclude other causes of liver disease including alcohol and drugs
- Imaging testing, starting with US to assess biliary tree
- Labs including: AMA, ANA, SMA, IgG, IgM
- Consider liver biopsy, especially if AST> 5x normal, or AMA ?

Natural History in the absence of ursodeoxycholic acid (UDCA)

- The 10-year survival of asymptomatic patients in 3 contemporary series ranged from 50-70%
- Once symptoms start, the median duration of survival ranged from 5-8 years
- Overall, the histologic stage progressed by one stage every 1.5 years

Natural History in the UDCA era

- In early-stage patients; survival rate was similar to that in the control population, in contrast, the probability of death or liver transplantation was significantly increased in patients treated in late stages of the disease.
- Overall; 10-years survival rate is 84%, and the 20-years survival rate is 66%
- The rate of histologic progression is significantly less in the UDCA group
- Bilirubin level is the best predictor of survival in PBC

Clinical Manifestations of PBC

- Fatigue: most common symptom, does not correlate with the severity, histologic stage, or duration of PBC
- May be a manifestation of untreated hypothyroidism which occurs about 20% of patients with PBC.

- **Pruritus**: more specific symptom than fatigue
- Formerly occurred in 20-70% of patients with PBC, It is now less common because of early stage diagnosis
- Usually worse at night while lying in bed, and is often exacerbated by contact with wool, other fabric, heat, or pregnancy

- **Sicca Syndrome** (dry eyes and/or mouth)
- **Cutaneous calcinosis**
- **Raynaud's phenomenon**
- **Dysphagia**

Unique manifestations of PBC

- **Portal HTN**: may develop in patients with early, precirrhotic PBC. These patients may develop Portal HTN-related complications despites having normal or near normal Liver synthetic function.
- Etiology: Nodular regenerative hyperplasia, which can be associated with obliteration of the portal venules and may lead to portal HTN in some of these patients.

Bone Disease

- Osteoporosis occurs in up to one-third of patients
- Patients with PBC appear to have “low-turnover” osteoporosis in which bone formation is inhibited and bone resorption is low or normal
- Vitamin D metabolism is normal in PBC except in advance disease and jaundice

Hyperlipidimia

- Serum lipids are strikingly elevated in PBC.
- Levels of HDL are typically elevated, and unusual lipoprotein particles, such as lipoprotein X, may accumulate
- High HDL/LDL ration PBC patients are not at increased risk of death from atherosclerosis

Hypothyroidism

- 20% of PBC patients.
- Needs annual screen

Vitamin Deficiency

- Clinically important deficiencies of Fat-soluble vitamins A,D,E, and K in PBC patients are uncommon, however, in severely jaundiced patient who are awaiting liver transplantation, clinical deficiency occur

Therapy

- **UDCA** in a dose 13-15 mg/kg/day is the only therapy for PBC approved by the U.S FDA
- The drug initiated gradually
- Patients with earlier histologic stage in general respond more favorably to UDCA, but even patients with advanced disease may derive improvement in survival or avoidance of need for liver transplantation with this therapy
- Cholestyramine or other bile acid binding sequestrants may interfere with UDCA absorption. Some antacids may bind bile acids, and so these should be administered at separate times.
- About 20% of patients will have normalization of liver biochemistries after 2 years

UDCA effects

- UDCA has been associated with reduction of LDL
- Reduced risk of developing varices and slower histologic progression
- UDCA therapy does not improve fatigue, pruritus, associated bone disease, or autoimmune features found in association with PBC

Symptomatic Management

- Fatigue: at this time there is no recommended treatment, although Modafinil seems promising.
- Pruritus: cholestyramine, rifampicin, naloxone, and others, [antihistamines use may be limited by the dry mouth side effects in patient with PBC and Sicca symptoms.
- Sicca syndrome: cyclosporine eye drops with aggressive mouth hygiene

Special cases

- AMA-negative PBC: diagnosis requires liver Bx.
- Overlap of AIH with PBC: can be simultaneously or sequentially
- AMA-positive AIH:

Case study 2

- 48 Y/O male from Southeast Alaska
- PMH: RA treated with MTX that was stopped in 02/10 due to elevated LFTs, HTN
- LABs: ALT/AST: 61/76, Alp: 407, T.Bili: 4.2, GGT: 576
- ANA: 1:160, SMA: 36, IgG: 3142, AMA: negative, IgG:363
- Liver Bx: ANMC pathology: severe portal inflammation, with numerours plasma cells, second opinion review from Myo Clinic: consistent with chronic biliary disease, not consistant with autoimmune hepatitis

Case study 2

- Treatment:
- Ursodiol titrated to 1500 mg daily.
- MTX was restarted.

- Follow up:
- AlP start to respond once Ursodiol dose increased to 1500 mg daily.
- AlT/AST normalized within few months.

Preventive care in PBC

- It is recommended to screen first degree relatives [particularly sisters and daughters] by checking Alp. And if elevated, check AMA.
- Checking LFTs q 3-6months in case AIH develop.
- TFT annually.
- Fat-soluble vitamins for patients with jaundice.
- Dexa scan.

Native persons with primary biliary cholangitis: An observational cohort study

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[1]Liver Disease and Hepatitis Program, Alaska Native Tribal Health Consortium

Methods

- The state wide Alaska Native Autoimmune Liver Disease Registry formed in 1998 was used to identify AN persons with PBC or a PBC-autoimmune hepatitis (AIH) Overlap disorder.
- Diagnosis of PBC was based on a positive anti-mitochondrial antibody (AMA), or a negative AMA with a liver biopsy compatible with PBC.
- The prevalence included patients from the registry who were alive on January 1st, 2015, and had AMA positive PBC, AMA negative PBC, or Overlap.
- Age adjusted point prevalence was calculated based on the 2012 year Alaska Native user population data for Alaska Area IHS, with 95% confidence intervals.

Methods

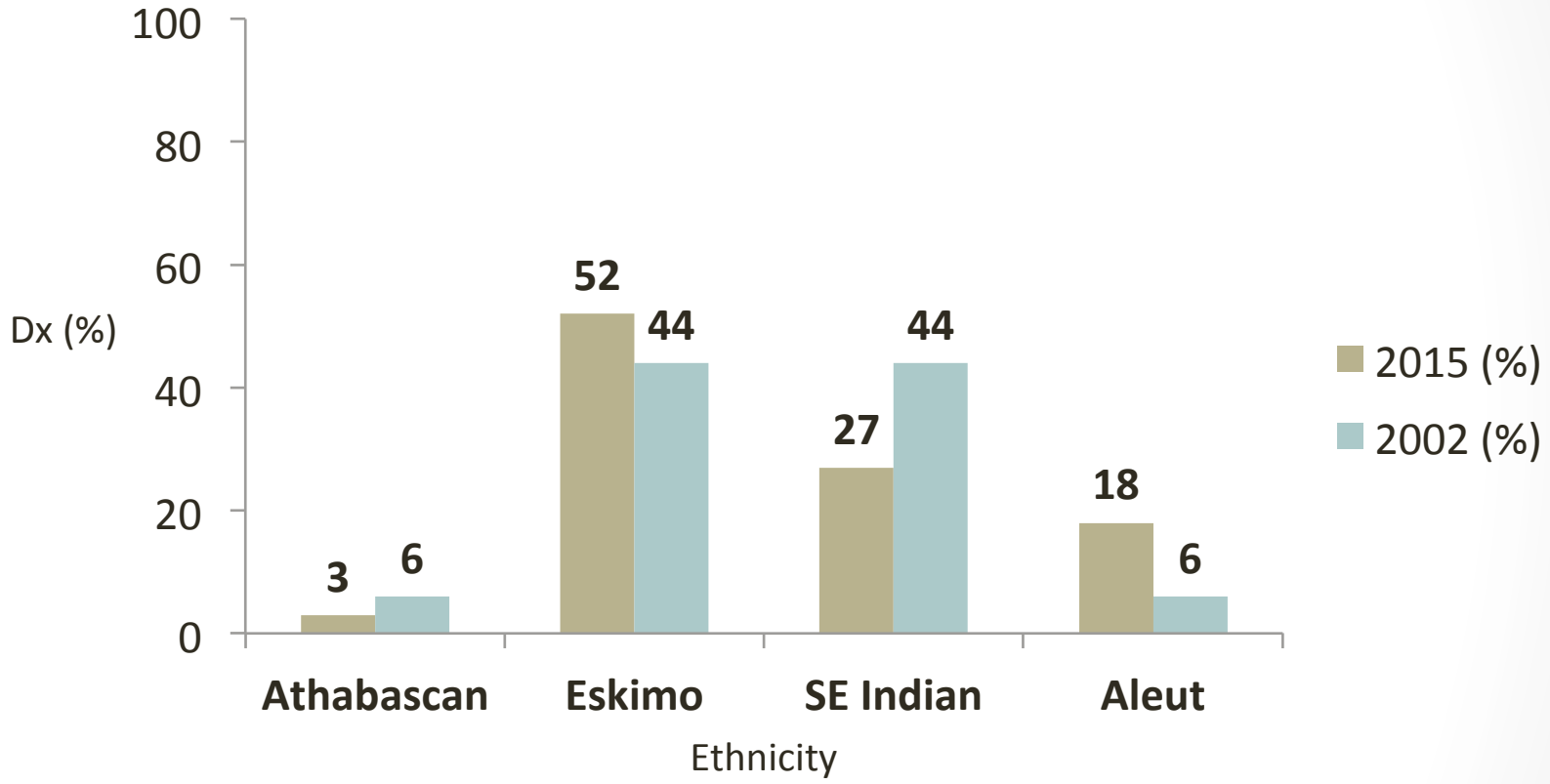
- Outcomes were examined in consented or dead patients from the registry, and were used to determine the rate of death due to liver related causes and the mean age of death.
- The mean length of treatment from the start of ursodeoxycholic acid (UDCA) until death or liver transplant was also determined.

Demographics

Total Cohort (n=112)		
Sex	Male	14 (12.5%)
	Female	99 (88.4%)
Age at Dx	20-40	21 (18.8%)
	40-60	63 (56.3%)
	>60	28 (25%)

Consented Cohort (n=88)		
BMI (n=76)	Normal (<25)	20 (22.7%)
	Overweight (25-29)	25 (28.4%)
	Obese (≥30)	20 (22.7%)
Other Autoimmune Disease	Yes	19 (21.6%)
	No	69 (78.4%)

Demographics Contd.



Age adjusted point prevalence of PBC in AN population as of January 1st, 2015

- **73.6** per 100,000 AN persons (95% CI: 57.9-89.4)

- **AN Men**: **23.9**/ 100,000 (95% CI 11.0-36.7)
- **AN Women: 121.8**/ 100,000 (95% CI: 93.4-150.2)

- **US Men**: **12.1**/ 100,000
- **US Women: 65.4**/ 100,000

Results

2015 Study

- Prevalence: **73.6/100,000** (95% CI: 57.9-89.4)
- Total PBC patients alive as of Jan 1, 2015: **88**
- The female to male ratio for Alaska Native People is **8.2:1**

2002 Study

- Prevalence: **16/100,000** (95% CI: 9.1-25.9)
- Total PBC patients alive as of Jan 1, 2002: **18**
- The female to male ratio for Alaska Native People: **18:0**

Long Term Outcomes

Average Follow up Period:
7.3 years
Range of Follow up Period:
1-25 years

All patients were treated with a clinically significant dose of UDCA*

(*one patient from consenting cohort (n=88) did not tolerate UDCA treatment, and was excluded*)

Average time from start of treatment until death:
6.6 years

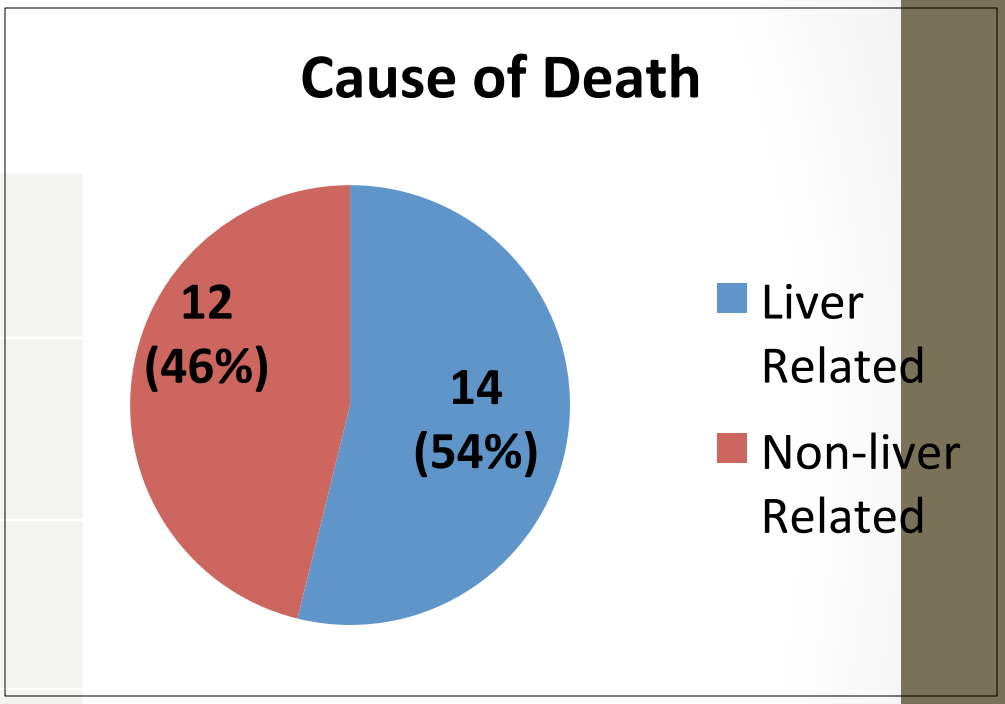
Long Term Outcomes Contd.

Mean age of death:
60.8 yo

Life expectancy for Alaska Native Population: **73.5 yo**

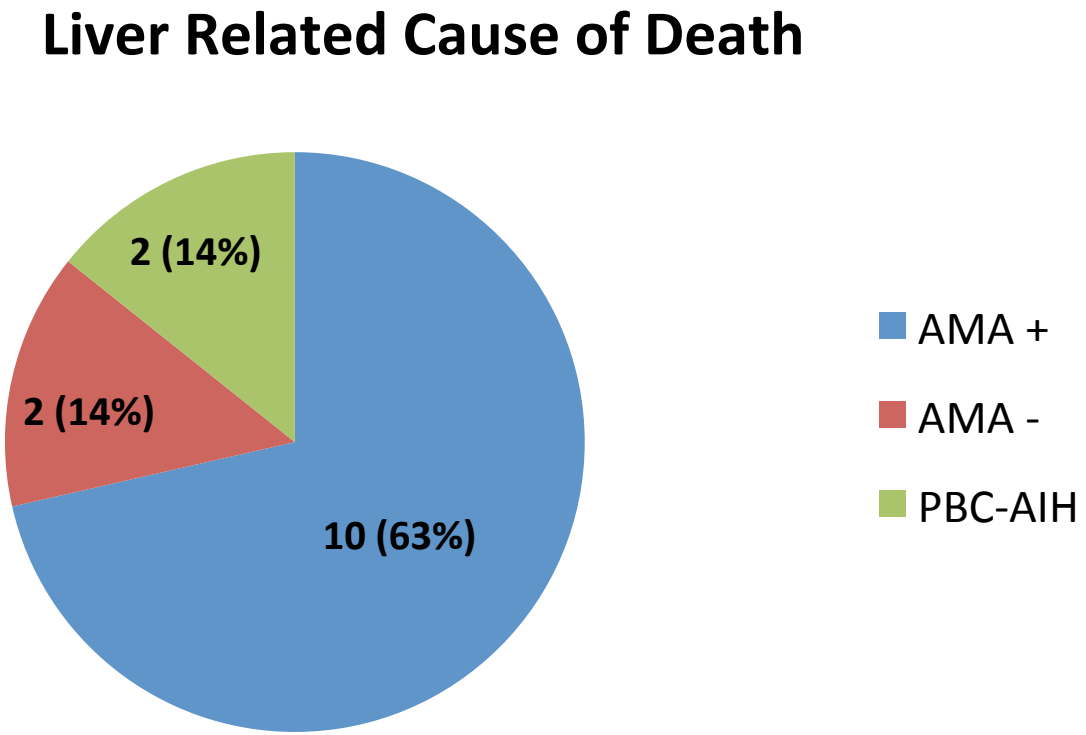
Life expectancy for Alaska White Population: **77.7 yo**

Life expectancy for U.S. White population: **78.3 yo**



12.7 years < Life expectancy for AN population

Long Term Outcomes Contd.



Majority of liver related deaths: **AMA+ PBC**

Conclusion

Prevalence of PBC within the Alaska Native population as of January 1st, 2015 is among the highest reported in literature

- *United States*: **40.2**/100,000
- *Newcastle, UK*: **24**/100,000
- *Umea, Sweden*: **15.1**/100,000

<< *AN population*: **73.6**/100,000 (95% CI: 57.9-89.4)