Programs to Manage Alaska Native Patients with Chronic Hepatitis B and C in Urban and Remote Rural Areas

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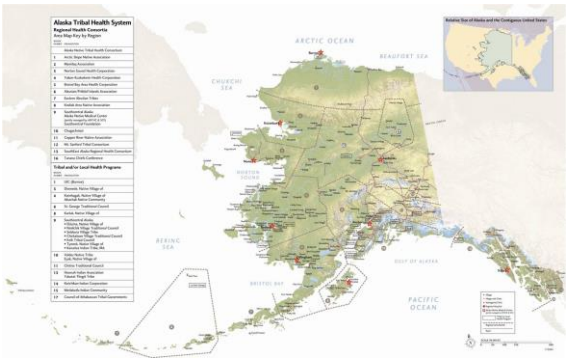
Background

- Alaska Native People have high rates of both HBV and HCV
- Many persons, especially with HBV, live in isolated communities
- Delivery care for chronic HBV and HCV is challenging
- Antiviral therapy to suppress HBV and cure HCV is available
- Surveillance for HCC can detect tumors at curable stage

Goals of My Talk

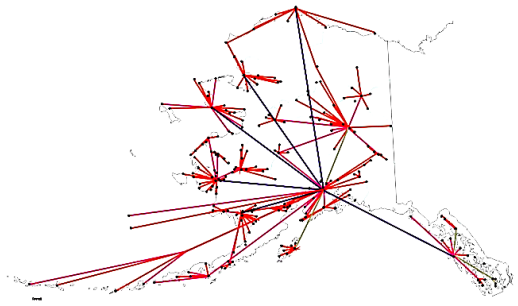
- Brief review of health care system for Alaska Natives
- How services with chronic hepatitis B and C are delivered for patients living in urban and very isolated rural communities
- Results of program to manage chronic HBV and HCV in Alaska
- Future plans for hepatitis services in Alaska
- How these programs might be adapted in other regional settings where indigenous populations are living in rural areas



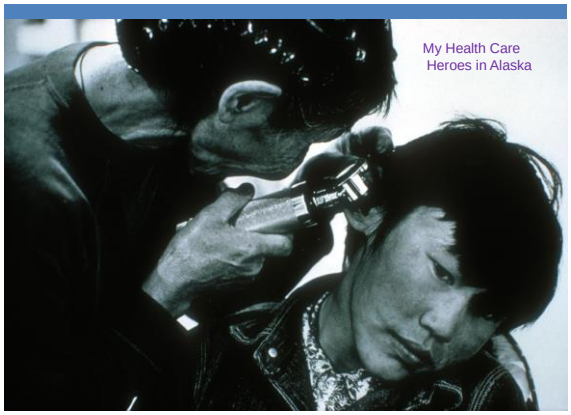
Alaska Native Health System

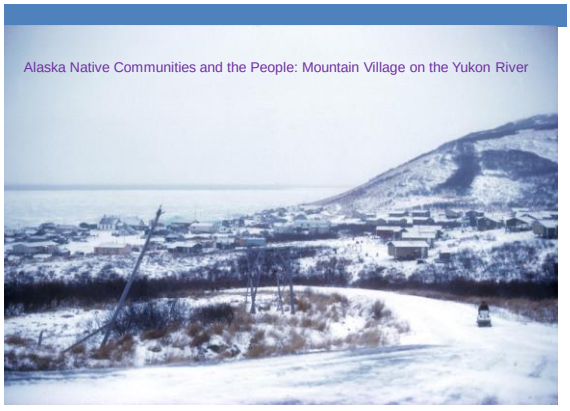
- Tribally owned and operated
- 45% of Alaska Native persons live in remote villages
  - Clinics there are staffed by Community Health Aides who receive 16 weeks of medical instruction
  - Air transportation usually needed to regional health facility for more intensive care
- Regional Hospitals and Clinics staffed with physicians and/or midlevel providers
  - Regional hospitals have lab and radiology facilities
- Tertiary Care hospital in Anchorage with primary care providers, specialists and regional laboratory and radiology capabilities

Village, Regional Hub Hospital/Clinics and Tertiary Hospital in Alaska

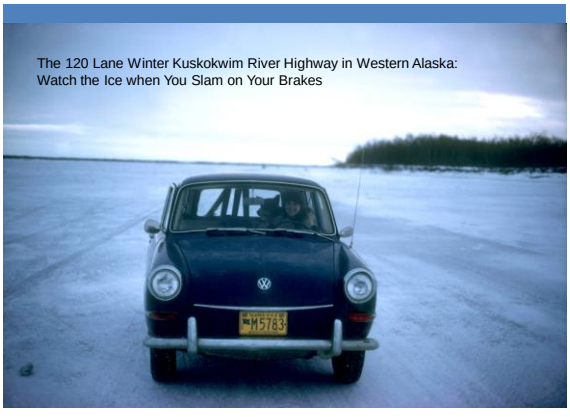


Distance is >4,000 km from east to west and >2,000 km from north to south


My Health Care
Heroes in Alaska


Alaska Native Communities and the People: Mountain Village on the Yukon River


How We Get Around in Rural Alaska
N5234U


The 120 Lane Winter Kuskokwim River Highway in Western Alaska:
Watch the Ice when You Slam on Your Brakes

Alaska Native Medical Center: A Tertiary Care Hospital in Anchorage

Components of Health Care Delivery for AN People with Chronic HBV and HCV

- Development of computerized registries
  - HBV since 1982
  - HCV since 1995
- Reminder letters to all infected persons to get blood tested in village or community clinic/hospital
- Liver Clinics in rural hospitals are conducted 1-2 times per year (From Barrow on the Arctic Ocean at the tip of North America to Ketchikan on the southern end of the Alaska panhandle)

Background: HBV

- From 1983-1987, 52,000 Alaska Native Persons were tested for hepatitis B seromarkers and 40,000 with negative markers were vaccinated.
  - 1560 persons with chronic hepatitis B virus (HBV) infection were identified
  - All identified persons have been followed prospective since then (median f/u 25 years)
  - Semiannual reminders to have blood drawn for AFP and HBV serology since 1983
  - LFT's and HBV DNA added in 2000

Chronic Hepatitis B

- We currently care for 1181 patients with chronic HBV
  - >75% live in rural communities, mostly western Alaska (Bristol Bay, Yukon-Kuskokwim, Norton Sound, Kotzebue Regions)

ANTHC Program to Follow Hepatitis B Carriers

- Reminder letters are sent every 6 months to all patient
  - List of Patients in community/region sent to provider with lab slip with bar code
- Blood drawn in village clinic or hospital then centrifuged and separated
- Sera mailed ANMC lab for liver panel, AFP
  - Results downloaded and reviewed by Hepatologist and HBV Registry RN who make evaluation and treatment decisions
  - HBeAg/anti-HBe tested once yearly
  - All patients had baseline testing for HBV DNA in 2001
- Patients with normal AFP results sent a letter, others with abnormal results are contacted by phone

Evaluation of Abnormal Results

- 40,385 Laboratory visits have been performed on persons with chronic HBV since 1982
- AFP cutoff: 10 ng/ml, patients with levels above referred to nearest facility for liver US
- Follow-up HBV DNA testing is performed At ANMC Molecular Biology laboratory in all high risk patients:
  - Patients with elevated ALT or AST
  - Those with personal or family history of HCC
  - Those with previous HBV DNA elevations above 2,000 IU/ml

Treatment of Immune Active Phase of HBV

- Persons with elevated ALT and HBV DNA >2,000 IU/ml levels are recommended for liver biopsy
- Persons with moderate to severe inflammation or fibrosis ≥ Metavir/Ishak 2 and those without liver biopsy with ALT > twice upper limit of normal and HBV DNA >20,000 treated as per AASLD Practice Guidelines*
- Currently only Tenofovir or Entecavir are used for initiation of treatment

Treatment of HBV in Alaska Native Persons

- 102 persons have received antiviral therapy
  - Since 2001 only 2 persons have developed decompensated cirrhosis, both had history of heavy alcohol usage.
- Those treated have LFT and HBV DNA levels done every 3 months till HBV DNA is negative (usually 1st year), then every 6 months
- Persons with HBV DNA present after 1 year or who go from negative to positive on treatment have testing for antiviral resistance

Screening HBV Infected Alaska Native Persons for HCC

- Persons with AFP > 10ng/ml are referred for to nearest hospital for ultrasound or Triphasic CT, reviewed by teleradiography
- To further evaluate suspicious lesions Triphasic CT or MRI
- Patients with small tumors have surgical resection or radiofrequency ablation.
  - 53 cases detected since 1982
    - 47 (89%) detected at potentially curable stage
      - 34 resected
      - 13 treated ETOH injection or RFA

Unadjusted OR, genotype and HCC (Alaska, 1983-2012)

	Incidence**	HCC OR	HCC 95% CI†
HBV Genotype			*p<0.001*
B/D	0.38	1.0	--
A	1.29	3.85	(1.16, 12.8)
C	5.52	17.4	(6.13, 49.4)
F	4.24	13.0	(5.18, 32.4)

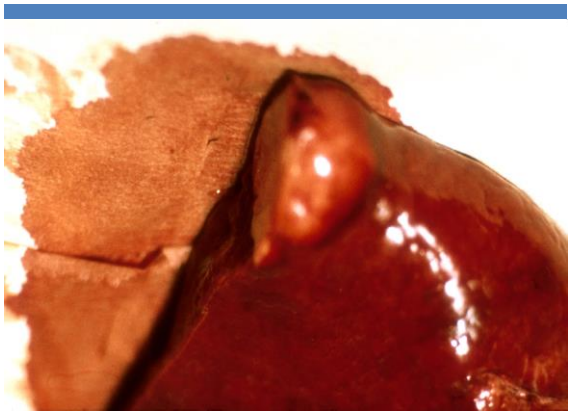
**HCC incidence is per 1000 person-years at risk.
†C.I. Confidence Interval.

HCC risk highest among genotypes C and F

Enhanced Ultrasound Surveillance to Detect HCC earlier in HBV

- Persons for whom liver Ultrasound surveillance recommended if living in a community that has US available
  - Persons with a family history of HCC
  - All Males over 40 years of age
  - All Females over 50 years of age
  - Persons with HBV genotype C over 40 years of age*
  - Persons infected with HBV genotype F at any age*
  - Persons over age 40 with high viral load (>20,000 IU/ml)

Increase risk of HCC in HBV genotypes C and F in Alaska Native Persons
Livingston: J Infectious Diseases 2007;195:5-11



Current and Planned Studies to Improve Patient Management of Chronic HBV Infection In Alaska

- Evaluation of inexpensive surrogate markers to identify persons with advanced liver fibrosis
  - APRI (AST and Platelet count)
  - FIB-4 (ALT, AST, age and platelet count)
- Effectiveness of AFP as a 1st screen assay to determine who needs liver ultrasound (including cost effectiveness for diagnosis of treatable HCC)
  - Cost per year of life saved in HCC screening program
- Translational studies to determine the cost effectiveness in preventing HCC and cirrhosis

Alaska Native Hepatitis C Registry

Update of the HCV cohort through June 29, 2014

Anti-HCV positive persons identified ANTHC database	2,557
Anti-HCV positive Alaska Natives/American Indians	2,454
Number of AN/AI Confirmed HCV Positive by RIBA or HCV RNA	2,170
Total number enrolled in study	1,381

Study participants who have been genotyped

Genotype 1	744 (63.3%); 90% 1a)
Genotype 2	217 (19.3%)
Genotype 3	157 (14.0%)
Genotype 4	5 (0.4%)

ANTHC Program to Follow Persons with Chronic Hepatitis C

- Reminder letters are sent every 6 months to all patient with lab slip with bar code to take to their local clinic
- We invite all persons to come to our field clinics conducted 1 to 3 times yearly at regional hospitals and clinics who are interested in antiviral therapy
- We assist providers in other hospitals to administer interferon-based and other therapy
- We use telemedicine for treatment and education
- All persons with cirrhosis receive a 2nd letter every 6 months to have liver US for HCC surveillance

Results of Testing Program

- In 2012 we mailed letters to 811 Anchorage patients:
  - 5% came back undeliverable,
  - 549 had (68%) an AFP/LFT done.
- Reminder letters are an effective way of having patients get laboratory testing for management of HCV to help decision making regarding antiviral therapy

HCV Results to Date

- 176 persons have received interferon-based antiviral therapy thru 2013
  - 92 have had a sustained virologic response (cure)
  - High drop out rate due to side effects
  - Most eligible patients do not want interferon
- We have started using the new direct acting oral antiviral agent

Goals for Next 3 Years: Detection of AN Persons with HCV

- Continue screening patients with risk factors for HCV
- Screen all AN persons born 1945-1965 (baby boomers)
  - Recommended by CDC and US Preventive Task Force
  - Putting a "reminder prompts" into medical record systems at Alaska Native Medical Center (ANMC) and Rural AN Regional Health Corporation hospitals
    - Sera drawn sent to ANMC lab; anti-HCV + specimens reflexed to HCV RNA and info downloaded automatically in our HCV database

HCV Management

- Ultimate Goal is to treat all Alaska Native Persons with chronic HCV as resources permit
  - Priority 1 Select good candidates with known advanced fibrosis to treat first
    - Using liver biopsy score or APRI >1.5; in future FibroScan
    - Perform Liver biopsy if extent of fibrosis unknown
    - Highest Priority:
      - Priority 1a: Childs B or C decompensated cirrhosis and those post liver transplant
      - Priority 1b: Childs A cirrhosis with platelet count <100,000, esophageal varices, elevated bilirubin or INR, AFP > 10 with normal US
      - Priority 1c: Patients with HCV/HIV co-infection
      - Priority 1d: Patients with serious extrahepatic HCV related disease
      - Priority 1e: All others with Child's A cirrhosis or bridging fibrosis

Patients to Treat for Hepatitis C

- Priority 2:
  - Priority 2a: Select good candidates with moderate fibrosis Using liver biopsy; Fibroscan?
  - Patients with diabetes and HCV
  - Patients with severe fatigue or arthritis
- Priority 3: Select good candidates with mild or no fibrosis: using liver biopsy or APRI < 0.5; Fibroscan?

Treatment Goals

- We plan to attempt to treat between 200-300 AN persons with HCV between January 2014 and December 2016
  - Target: at least 50% have advanced fibrosis
- Reduce the incidence of in cohort of persons with HCV
  - Those with SVR vs. untreated
  - Overall incidence from 2013-2018 vs. through 2012
  - Relative Risk of dying of HCC in the entire AN population

Evaluation of Effectiveness of HCV Treatment Program

- Examine incidence of Adverse outcomes, ESLD, HCC and LRD, from HCV during three different time periods
  - Through 2005 (Gastroenterology 2010;138:922-31)
    - Period on availability of IFN/Ribavirin; 36 pts. treated
  - Currently analyzing incidence of ESLD, HCC and LRD from 2006 to 2012: 118 pts. treated
    - Period of availability of Peg-IFN/Ribavirin
  - 2013 to 2018
    - Period of availability of direct acting antiviral agents (DAA)

LiverConnect Videoteleconference

- 1st Tuesdays, 8-9am Alaska Standard Time
- Case study presentations from rural providers
- CEUs (1.0 for each session)
- Contact Ebba Paniptchuk to join: +1 907-729-1560
- Questions: Email liverconnect@anthc.org or contact Julia Plotnik, RN +1 907-729-1581 or Jim Gove, RN +1 907-729-1568

Liver Disease/Hepatitis Program Website

http://www.anthctoday.org/community/hep/index.html

- Initial Funding from Government
- Reviewed quarterly by our advisory group of indigenous patients living with HCV
- Contents of Website
  - Patient Information
  - Provider Information
  - Hepatitis C Treatment
  - Publications
  - LiverConnect – Past presentations
  - The website is constantly updated as new treatments

Public Health Usefulness of Registries

- Reminder letters also can include educational information, such as:
  - Recommendations for screening for other virus (Hepatitis A screening and vaccination)
  - Useful educational information about hepatitis infection: for example new treatments
  - Information for family members and close contacts
  - Information for referral options for management

Conclusions

- The ANTHC Program for the management of Hepatitis B and C has been shown to be an effective way to identify persons living in remote communities who need antiviral therapy and diagnose HCC at a potentially curable stage
  - Cost effective analysis studies are planned for this program
  - Research on better markers to identify persons with HCC and ongoing liver disease are needed

WHO Guidelines for Hepatitis B & C

- Using PICO format (Population, Intervention, Comparison, Outcome)
  - Makes recommendations based on strength of evidence and clinical practice
    - Recommendation can be strong, moderate or weak or against
    - Evidence can be high, moderate, low, very low
- Hepatitis C recommendation published
- Hepatitis B to be published early 2015
  - Components:
    - All persons with HBV should be followed a minimum of once yearly
    - Decisions on recommendations for treatment will be based on ALT and HBV DNA in absence of liver biopsy
    - In absence of HBV DNA clinical or serologic or radiographic (US or Fibroscan) evidence of cirrhosis