Helicobacter in the NorthWest Territories: the Aklavik project

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Justin Cheung, Amy Morse
For the Aklavik Project Team
Objectives

- To learn about some important medical facts of *Helicobacter pylori*
- To learn about the association between *Hp* and gastric cancer
- To describe the Aklavik *Hp* project in NWT
- To learn about treatment of *Hp*
Hp infection Life Time Risk

- Antral predominant gastritis > 85%
- DU 5-15%
- GU < 5%
- Gastric cancer < 1%
Outcomes of *H. pylori* colonization

- 5-15% Duodenal or Gastric ulcer
- < 1% gastric cancer
- 85% gastritis (dyspepsia?)
Hp Prevalence in Canada

- 25-30% infected
- In 1980s risk was 6-8% per decade
- Prevalence decreasing in younger population
Gastritis is the Disease
Ulcers and Cancer are secondary phenomena
Gastric Cancer risk factors

- Smoking
- Diet
- Age
- Helicobacter
- Pernicious anemia
- Genetic factors → E-cadherin
1526 Japanese patients with DU, GU, gastritis, NUD
1246 Hp pos, 280 Hp-neg.
endoscopy baseline and at 1-3 years

gastric cancer N=36 (2.9%)

(-) NUD 4.7%
(-) GU 3.4%
(-) polyps 2.2%
(-) DU 0%

Proportion Free of Gastric Cancer

Year of Follow-up

H. pylori-negative

H. pylori-positive

No. at Risk

H. pylori-negative  
280  272  251  245  213  57

H. pylori-positive  
1246  1219  1086  907  782  258

Uemura, NEJM 2001
Normal Body Mucosa
Body Gastritis with Atrophy
Normal gastric epithelial cells.

Intestinal (goblet cell) metaplasia
High Grade Dysplasia
(Early Gastric Cancer)
# Hp-Gastric Cancer Relative Risk

<table>
<thead>
<tr>
<th>ATROPHY</th>
<th>Gastritis Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>none/mild</td>
<td>antral predominant 1.0</td>
</tr>
<tr>
<td>moderate</td>
<td>pangastritis 15.6</td>
</tr>
<tr>
<td>severe</td>
<td>corpus predominant 34.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intestinal metaplasia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>absent</td>
<td>1.0</td>
</tr>
<tr>
<td>present</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Gastric Cancer

- Progressive gastritis body
- Acid Output decreases

Intestinal metaplasia
atrophy

Gastric cancer
Aklavik *H. pylori* Project
A CRY FOR HELP
Northern Canada

Political Definition
• Northern Territories
  • Nunavut
  • NWT
  • Yukon

Geographic Definition
• North of Tree Line (includes Canada’s geographic centre)
  • Most of Nunavut
  • Northern parts of
    • NWT
    • Yukon
    • Manitoba
    • Ontario
    • Quebec
    • Labrador

http://images.google.com/ Map_Canada_political-geo.png
People of Northern Canada

- 2006 Population
  - Nunavut 29,474
  - Northwest Territories 41,464
  - Yukon 30,372
Study Community: Aklavik, NWT

**Location:**
- On Peel Channel of Mackenzie River Delta
- North of Arctic Circle
- 113 km south of Arctic coast
“With our lives, it’s all about the journey. With our luggage, it’s definitely about the destination.”
Why Aklavik?

- Selected by NWT health authorities as a starting place for this research
  - High level of community concern due to stomach cancer deaths in some families
  - Enthusiasm for the research from local health authorities
- Other communities to be included later for comparison
Research Context

- NWT communities express concern about health risks from *H. pylori* infection and seek research to find solutions.
- NWT health authorities seek information to improve management of *H. pylori* infection given perception of frequent treatment failure.
- NWT government seeks evidence to inform public health policy related to *H. pylori* infection.
- Many NWT communities are remote with respect to advanced medical services.
CANHelp Working Group
Research Program Goals

• Collaborative Infrastructure Development
  • University of Alberta, NWT Government, Northern Health Services Network, Community Leaders

• Link with Circumpolar H. pylori Researchers
  • Alaska, Greenland

• Initial Research Project
  • Aklavik H. pylori Project

• Expand Research to other Northern Communities

• Policy Analysis and Knowledge Transfer
Research Collaboration

Aklavik Community Organizations
- Rachel Munday, Nurse in Charge, Aklavik Health Centre
- Aklavik Health Committee
- Billie Archie, Arctic Health Research Network, Aklavik Chapter

NWT Agencies
- Andre Corriveau, Chief Medical Officer, Health and Social Services, NWT
- John Morse, Medical Director, Stanton Territorial Health Authority
- Leah Seaman, Beaufort-Delta Regional Health and Social Services Authority
- Susan Chatwood, Director, Arctic Health Research Network

Capital Health
- Robert Bailey, Director, Northern Health Services Network

University of Alberta
- Principle Investigator: Karen Goodman, Epidemiology
- Gastroenterology: Justin Cheung, Sander van Zanten, Richard Fedorak, Amy Morse
- Pediatric Gastroenterology: Hien Huynh
- Microbiology: Monika Keelan, Joanne-Simala Grant, Robert Rennie
- Pathology: Safwat Girgis
- Anthropology: Christopher Fletcher
- Health Policy: Carl Phillips
Few Data on *H. pylori*-associated Disease in Northern Populations

- **Peptic Ulcer Disease**
  - Increased ratio of gastric ulcer to duodenal ulcer
    - Inuit of northern Labrador (*William 1985*)
    - Observed in 3 other studies
  - Increased hospitalizations for peptic ulcer disease diagnoses
    - Registered Indians in Manitoba (province-wide data for 1989-1993 had nearly twice the national rate of other persons (*Bernstein 1999*))
Gastric Cancer in Northern Populations of North America

- **4th most frequently diagnosed cancer** in NWT males in contrast to 10th for males across Canada

- Age-adjusted incidence rate for NWT males twice Canadian rate (higher for regions with predominantly Aboriginal populations)

- In Dene (Athabascan First Nations) males, tied for 3rd place with prostate at 7% of cancers diagnosed; 10% of cancer deaths

- In Inuit males, 2nd after lung at 16% of cancers diagnosed
Stomach Cancer in US Men, 1988-92

Racial/Ethnic Patterns of Cancer in the United States. SEER Monograph. 1996

Mortality rates unavailable: Alaska Native, Korean, Vietnamese
### H. pylori Prevalence in Northern Canada & Other Circumpolar Populations

<table>
<thead>
<tr>
<th>Place</th>
<th>Population</th>
<th>Age (yrs)</th>
<th>n</th>
<th>HP+%</th>
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</thead>
<tbody>
<tr>
<td>Northern Quebec</td>
<td>Hodgins 1998</td>
<td>Maternal</td>
<td>100</td>
<td>27</td>
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<tr>
<td>Northern Manitoba</td>
<td>Bernstein 1999; Sinha 2002</td>
<td>Adult</td>
<td>306</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-12</td>
<td>163</td>
<td>56</td>
</tr>
<tr>
<td>Nunavut</td>
<td>McKeown 1999</td>
<td>All ages</td>
<td>256</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-15</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Chutkotka, Russia, Reshetnikov 1998</td>
<td>Chutkotka Native coastal Arctic village, males</td>
<td>Mean=32</td>
<td>34</td>
<td>77</td>
</tr>
<tr>
<td>Nuuk, Greenland</td>
<td>Milman 2003</td>
<td>22-76</td>
<td>71</td>
<td>47</td>
</tr>
<tr>
<td>Sisimiut, Greenland</td>
<td>Koch 2005</td>
<td>15-87</td>
<td>685</td>
<td>58</td>
</tr>
<tr>
<td>Norton Sound, Alaska</td>
<td>Zhu 2006</td>
<td>All ages</td>
<td>610</td>
<td>80</td>
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<tr>
<td></td>
<td></td>
<td>0-24</td>
<td></td>
<td>72</td>
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</tbody>
</table>
Study Community: Aklavik, NWT

- 2004 population: 631
  - 90% Inuvialuit (Inuit) or Gwich’in Dene (First Nation)

- Access
  - Reached only by air or by winter ice-road from Inuvik
Aklavik *H. pylori* Project
Logo Contest Prize Winner (Child)
Project Goals

- To address community concerns about health risks from *H. pylori* infection
- To recommend *H. pylori* management strategies to health authorities
- To reduce health risks from *H. pylori* infection
Research Questions

• How widespread is the infection?
• What environmental factors are associated with it?
• What health problems result from it?
• Who requires medical care related to it?
• What are the best ways to treat it?
• How can it be assessed in remote communities?
• How can communities be protected from it?
Aklavik *H. pylori* Project Specific Aims

Investigate *H. pylori* infection in Aklavik

- **Screen residents** for *H. pylori* infection, family history, symptoms
- **Collect epidemiologic data** on risk factors for *H. pylori* infection
Aklavik *H. pylori* Project Specific Aims

- **Offer upper endoscopy to:**
  - Estimate the prevalence of endoscopically significant abnormalities
- **Obtain biopsies to:**
  - Estimate the prevalence of *bacterial resistance* to antibiotics and bacterial virulence factors
  - Characterize *histopathology* in relation to *H. pylori* infection
- **Evaluate the effectiveness of anti-*H. pylori* therapies**
- **Follow those treated long-term to identify factors associated with treatment failure and re-infection**
Susie Husky
Health Centre
Naniliruat Ikayuqtiihiugvi
Srii Gwindáih Zheh
Aklavik *H. pylori* Project Participation

- Participants recruited: 314
- Clinical surveys completed: 314
- Individuals with breath test results: 246
- Aklavik residents appearing for endoscopy: 197
- Individuals from whom biopsies were obtained: 193
- Epidemiology surveys completed to date
  - Household: 74
  - Individual: 119
RCT Transnasal Endoscopy

- Unsedated, Olympus GIF-N180 4.9mm diameter
- Xylocaine administered as a spray (XS) versus topical xylometazoline administered as a jelly (XJ) plus xylocaine

Outcomes:
- Patient comfort (=)
- Physician ease endoscopy (XJ > XS)
- Procedure time (22 vs 19 min)
Aklavik *H. pylori* Project

**H. pylori** Prevalence

- Proportion positive on breath test:
  - **56%** (137/246)
- Preliminary positive result on biopsy culture:
  - **72%** (140/195)
Endoscopic findings

- Esophagitis: n = 20
- Barrett's esophagus: N = 5
- Gastric Erosions: N = 12
- Gastritis: N = 27
- Gastric Ulcer: N = 6
- Duodenal erosions: N = 1
- Duodenitis: N = 13
- Duodenal ulcer: N = 0 (surprising)
Histology (n=184)

- Sydney classification was used

- **Gastritis**
  - SEVERE 43%  
  - MODERATE 47%  
  - MILD 10%

- **Hp density**
  - 3+ 36%  
  - 2+ 37%  
  - 1+ 27%

- Atrophic changes 14%

- Intestinal metaplasia 16%
- Gastritis much more severe than seen in Edmonton
Aklavik Project Funding Agencies

- Alberta Heritage Foundation for Medical Research
- Canadian Association for Gastroenterology with Canadian Institutes for Health Research / AstraZeneca
- Social Sciences and Humanities Research Council
- Public Health Agency of Canada
- Indian and Northern Affairs Canada
- Canadian Circumpolar Institute
Aklavik Project Supporters
“Fortunately, treatment will be relatively inexpensive, since you have the generic form of the disease.”
 Twice daily PPI triple therapy

PPI- Clarithromycin and Amoxycillin (PPI-CA)
PPI- Clarithromycin and Metronidazole (PPI-CM)

are equally effective  > 70-80 %
How is *Hp* killed?

- ???
- PPI decreases MIC some antibiotics
- Some antibiotics can cross gastric mucosa
- Direct anti-*Hp* effect in stomach or absorption first and then secretion into gastric lumen?
How do PPIs work in *Hp* Treatment?

- Direct anti-*Hp* effect
- Increase killing capacity antibiotics (MIC) by raising pH
  - Clarithromycin and Amoxycillin MIC increase x10
  - Metronidazole no effect
- Change gastric milieu
  - Gastric juice volume
### Effect PPI

**MACH2 Study (N=514)**

<p>| | | |</p>
<table>
<thead>
<tr>
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<tr>
<td>CM</td>
<td>69 %</td>
<td></td>
</tr>
<tr>
<td>OCM</td>
<td>87 %</td>
<td>GAIN 18%</td>
</tr>
<tr>
<td>CA</td>
<td>26 %</td>
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<tr>
<td>OCA</td>
<td>94 %</td>
<td>GAIN 68%</td>
</tr>
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</table>

Gastroenterology 1999;116:248-253
Pre Primary treatment Resistance Over Time

Percent:

- **CLA**
- **MET**

Year:
- NS 1995-96 (MET NA)
- NS 1997-98
- NS 1999-01
- NS 2002-04
- Can 1999

Legend:
- **CLA**
- **MET**
Quadruple therapy

Second Line

7-14 days

Most data: PPI-BMT  →  75-80 %

- PPI bid
- Bismuth qid
- Metronidazole 250-500mg qid
- Tetracycline 500mg qid

APT 2002;16:1047-1057
Levofloxacin based Triple Rx

- PPI bid
- Amoxycillin 1g bid
- Levofloxacin 500 mg bid

- In Italy > 80%
- In Canada ?, USA ?
Sequential Therapy

- PPI bid
  Amoxycillin 1 g bid } x 5 days

- PPI bid
  Clarithromycin 500 mg bid } x 5 days
  Metronidazole 500mg bid
Table 1  Overall eradication rate following sequential therapy at intention to treat (ITT) and per protocol (PP) analysis

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>Centres involved</th>
<th>Patients enrolled</th>
<th>Patients cured</th>
<th>ITT (%)</th>
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<td>Zullo et al&lt;sup&gt;P2&lt;/sup&gt;</td>
<td>2000</td>
<td>1</td>
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<td>2</td>
<td>63</td>
<td>61</td>
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<td>2002</td>
<td>1</td>
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<td>90</td>
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<td>Zullo et al&lt;sup&gt;P4&lt;/sup&gt;</td>
<td>2003</td>
<td>8</td>
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<td>Hassan et al&lt;sup&gt;P5&lt;/sup&gt;</td>
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<td>1</td>
<td>174</td>
<td>166</td>
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<td>Francavilla et al&lt;sup&gt;α0&lt;/sup&gt;</td>
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<td>Vaira et al&lt;sup&gt;κ5&lt;/sup&gt;</td>
<td>2007</td>
<td>2</td>
<td>146</td>
<td>133</td>
<td>91.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1805</td>
<td>1687</td>
<td></td>
<td>93.5</td>
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</tbody>
</table>
RCT Sequential vs PPI-CA

- N = 300

- Results

  **Sequential** 89%
  **PPI-CA** 77%

<table>
<thead>
<tr>
<th></th>
<th>Sequential</th>
<th>PPI-CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clari-R</td>
<td>8/9 (89%)</td>
<td>6/21 (29%)</td>
</tr>
<tr>
<td>Clari-S</td>
<td>108/114 (95%)</td>
<td>86/91 (95%)</td>
</tr>
</tbody>
</table>

Ann Intern Med 2007;556-563
Conclusion

- Levofloxacin based therapies and sequential therapy need to be evaluated in Canada
- Clarithromycin resistance is the Achilles heel of current therapies
Hp Resistance Aklavik

- 33% Metronidazole resistance
- 13% Clarithromycin Resistance
- 4% both C and M
Objectives Treatment Trial

- Identify most effective *H. pylori* therapy for Aklavik
- Treat based on resistance data
- RCT in Rx naïve patients
  - Conventional PPI-CA therapy vs Sequential therapy x 10 days
- Examine the effect of adherence to medication regimens and other clinical and demographic factors on treatment success.
Treatment Allocation

**RCT**

- 53 Rx for PPI-AC
- 55 Rx for Sequential therapy

*Based on Resistance data*

- 10 Rx for Quadruple therapy
Conclusions

- Working with the Aklavik community has been rewarding and is feasible
- There is a very high prevalence of *Hp*
- The histologic gastritis in Aklavik is more severe than in Edmonton
- Epidemiological research and RCTs will help establish how we can manage the *Hp* related burden of illness in Aklavik
“He’s bipolar.”