Community-driven research on Helicobacter pylori infection in Northern Canada

Canadian North Helicobacter pylori (CANHelp) Working Group

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The Agenda...

• *H. pylori* in the North

• Who is the CANHelp Working Group?

• Overview of Community Projects

• Project Components

• Findings to Date

• Current Lab Projects
H. pylori in the North

- High prevalence (~50-95%) in circumpolar north
- Treatment failure is common
- Gastric cancer is the 4th most frequently diagnosed cancer in NWT males vs 10th for males across Canada
- Few community-based studies of H. pylori in northern Canada
CANHelp (Canadian North Helicobacter pylori Working Group)

- Multidisciplinary group formed in 2006 in response to:
  - Community concerns about health risks from *H. pylori* infection
  - Health care providers seeking information to improve clinical management of *H. pylori* infection
  - Public health officials wanting evidence to inform public health policy related to *H. pylori* infection
The CANHelp Working Group aims to:

- Describe disease burden and risk factors associated with *H. pylori* infection
- Develop clinical management approaches to reduce health risks from *H. pylori* infection
- Develop knowledge exchange strategies that help foster a great understanding of health risks associated with *H. pylori* infection, as well as solutions and unsolved challenges for reducing these risks.
Community *H. pylori* Projects

Aklavik (2007)  
Tuktoyaktuk (2010)  
Old Crow (2008)  
Fort McPherson (2011)
Project Components

Adapted with guidance from a project planning committee in each community:

- Community Survey
  - *H. pylori* screening by UBT
  - Clinical/epidemiologic data collection
- Endoscopy
- Treatment
- Knowledge Exchange
- Policy Development
## Project Data

<table>
<thead>
<tr>
<th>Community Projects</th>
<th>UBT Results</th>
<th>Gastric Biopsies</th>
<th>Post-treatment UBT</th>
<th>H. pylori Isolates</th>
<th>Antibiotic Resistance Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aklavik (Population ~590)</td>
<td>332</td>
<td>194</td>
<td>111</td>
<td>139</td>
<td>118</td>
</tr>
<tr>
<td>Old Crow (Population ~250)</td>
<td>194</td>
<td>63</td>
<td>63</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Tuktoyaktuk (Population ~900)</td>
<td>103</td>
<td>13</td>
<td>15</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Fort McPherson (Population ~800)</td>
<td>209</td>
<td>52</td>
<td>54</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>838</strong></td>
<td><strong>322</strong></td>
<td><strong>243</strong></td>
<td><strong>229</strong></td>
<td><strong>203</strong></td>
</tr>
</tbody>
</table>
Endoscopy Component (Aklavik)

- Targeted residents aged >15 years old
- Endoscopies performed in Health Center by visiting gastroenterologists
- Equipment transported temporarily to Health Center
- Thin gastrosopes, without sedation
- 5 gastric biopsies obtained from each participant for histopathology
  - 2 antrum, 2 corpus, 1 incisura
- 2 gastric biopsies obtained for culture
- Biopsies transported back to Edmonton
- Histopathology: FFPE were stained with H&E and Giemsa then evaluated by one pathologist using updated Sydney system
- Microbiology: *H. pylori* culture, antimicrobial susceptibility testing, genotyping
Findings to Date: *H. pylori* Prevalence

<table>
<thead>
<tr>
<th>Community project</th>
<th><em>H. pylori</em> prevalence by UBT</th>
<th>% positive</th>
<th>Number with results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aklavik, NT</td>
<td>58</td>
<td>332</td>
<td></td>
</tr>
<tr>
<td>Old Crow, YT</td>
<td>66</td>
<td>194</td>
<td></td>
</tr>
<tr>
<td>Tuktoyaktuk, NT</td>
<td>57</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Ft. McPherson, NT</td>
<td>59</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>60</strong></td>
<td><strong>838</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Findings to Date: Histopathology

<table>
<thead>
<tr>
<th>Chronic Gastritis</th>
<th>Aklavik (n=129)</th>
<th>Old Crow (n=57)</th>
<th>Tuktoyaktuk (n=8)</th>
<th>Ft McPherson (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>9</td>
<td>4</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>47</td>
<td>32</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>Severe</td>
<td>43</td>
<td>65</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Atrophy</td>
<td>21</td>
<td>74</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>Intestinal Metaplasia</td>
<td>11</td>
<td>35</td>
<td>38</td>
<td>14</td>
</tr>
</tbody>
</table>
Findings to Date: Treatment

Treatment trial:

- Standard treatment (Hp-pac)
  - PPI with clarithromycin and amoxicillin for 10 days

- Sequential treatment
  - PPI and amoxicillin for days 1-5
  - PPI with metronidazole and clarithromycin for days 6-10

- Quadruple treatment
  - PPI, peptobismol, metronidazole, and tetracycline for 10 days
Findings to Date: Treatment

Treatment success by regimen and community among treatment trial participants:

<table>
<thead>
<tr>
<th>Community</th>
<th>% Successfully Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triple</td>
</tr>
<tr>
<td>Aklavik, NT</td>
<td>62 (29/47)</td>
</tr>
<tr>
<td>Old Crow, YT</td>
<td>-</td>
</tr>
<tr>
<td>Tuktoyaktuk &amp; Ft. McPherson, NT</td>
<td>-</td>
</tr>
<tr>
<td>TOTAL</td>
<td>62 (29/47)</td>
</tr>
</tbody>
</table>
Findings to Date: Antibiotic Resistance

Antibiotic resistance by antibiotic among participants with *H. pylori* isolates from gastric biopsies:

| % of *H. pylori*-positive Participants with Isolates Resistant to Specified Drug (95% CI) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Amox                           | Cipro                           | Clari                           | Metro                           | Nitro                           | Rifam                           | Tetra                           |
| **Total for all communities (n=203)** | **0 (0-1.5)***               | **3.9 (1.7-7.6)**               | **16 (11-22)**                 | **35 (28-42)**                  | **1.0 (0.1-3.5)**               | **1.5 (0.3-4.3)**               | **0.5 (0.01-2.7)**               |

CI, confidence interval

*One-sided 95% CI
Findings to Date: Antibiotic Resistance

Multiple-drug resistance by community (and year) among participants with *H. pylori* isolated from gastric biopsies:

<table>
<thead>
<tr>
<th>Community (n, Year of Biopsy)</th>
<th>% of Participants with <em>H. pylori</em> Isolates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To any 1 antibiotic</td>
</tr>
<tr>
<td>Aklavik, NT (n=118, 2008)</td>
<td>25 (18-34)</td>
</tr>
<tr>
<td>Old Crow, YT (n=53, 2012)</td>
<td>30 (18-44)</td>
</tr>
<tr>
<td>Tuktoyaktuk &amp; Ft. McPherson, NT (n=32, 2013)</td>
<td>53 (35-71)</td>
</tr>
<tr>
<td>TOTAL (n=203)</td>
<td>31 (25-38)</td>
</tr>
</tbody>
</table>
Findings to Date:
Treatment Success with Antibiotic Resistance

Treatment success by regimen among participants with antibiotic-resistant isolates:

<table>
<thead>
<tr>
<th>Isolates Resistant to Specified Drug</th>
<th>% Successfully Treated (95% CI) n (number treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triple</td>
</tr>
<tr>
<td>All participants with resistant isolates</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Participants with resistant isolates in treatment trial (randomized to regimen)</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>
Findings to Date: Summary

Relative to residents of Edmonton, Alberta, Indigenous residents of Aklavik, NT have a high prevalence of *H. pylori* infection with elevated frequencies of:
- Erosions and ulcers of the gastric corpus relative to the duodenum
- Severe gastric inflammation
- Gastric atrophy

- A bismuth-based 4-drug therapy appears much more effective than the more commonly used treatments in Canada, but more data is needed.

- Treatments are burdensome, which can lead to problems with compliance.

- Follow-up *H. pylori* testing in Aklavik suggests most people who were successfully treated have remained *H. pylori* free.
Current Projects

• Relatedness of *H. pylori* isolates across households and multi-household groups (Household study)

• Detection of *H. pylori* in environmental water samples

• Whole genome sequencing
Household Study: Background

- **Objective**: To determine the genetic relatedness of *H. pylori* isolated from Aklavik family groupings by multi-locus sequence typing (MLST)
  - Housekeeping genes (*atpA, ureI, trpC, mutY, yphC* and *ppA*) and a virulence gene (*vacA*) were sequenced and aligned to a PUBMLST reference sequence.
- **Participants from households where 2+ members had *H. pylori* isolated by culture**
  - 54 participants belonging to 25 households
  - Extended-family kinship groups identified by anthropologist
- **Maximum likelihood phylogenetic trees generated for each gene and concatenated sequences of all genes**
  - Nucleotide and translated sequences +/- vacA
  - Examined how isolates fell on tree to determine if clustered according to family groupings.
Household Study: Results

• Concatenated sequence analysis identified 24 *H. pylori* sequence types (STs)
  • 17 unique STs
  • Other isolates shared identical STs (excluding *vacA*)
    
  2 (ST2960)  3 (ST2925)  3 (ST2933)  4 (ST2934)  5 (ST2988)  8 (ST2945)  12 (ST2929)

• There are defined clusters

• Can compare phylogenetic trees to “Kinship Trees” generated by the anthropologist on the team
Detection of *H. pylori* in Environmental Water Samples

- Community has expressed concern that *H. pylori* may be present in water
  - Waste water is stored in sewage lagoon
  - Annual flooding provides opportunity for contamination of other bodies of water

- Preliminary study failed to detect *H. pylori* in environmental water samples by culture or PCR except for weakly positive PCR from sewage lagoon sample

- Current studies focused on improved strategies to concentrate water samples to improve detection of *H. pylori*
  - Validate methods in local treated and environmental samples spiked with *H. pylori*
    - Improve water filtration methods & Increase sample volumes to concentrate samples
    - DVC-FISH methods to detect viable *H. pylori* in environmental samples
  - Test validated methods in the field
Whole Genome Sequencing

• Collaboration with Doug Berg

• RAPD DNA fingerprinting of Aklavik isolates
  • 52/57 in 6 distinct groups

• Whole genome sequencing on two Amerind *H. pylori* strains
  • 1 from most unique RAPD/MLST type and other from most abundant RAPD/MLST type
  • each contained typical *H.pylori* chromosome and 2 unrelated plasmids and lacked *cag* pathogenicity islands (as do all Aklavik Amerind strains)

• The strain representing the abundant RAPD/MLST type has 2 unique features
  • Iron dependent urease genes next to *cheW*
  • 140 rearrangements relative to Aklavik A117 and other sequenced strains
  • Novel lineage !?
Next Generation Sequencing of *H. pylori* Genomes

In Progress:

- 4 isolates sequenced by a UAlberta core facility using the Illumina MiSeq platform
  - NexteraXT Libraries
  - 500 cycle v2 nano MiSeq run
  - 300bp Paired end reads
Acknowledgements

CIHR Institute of Aboriginal People’s Health

CIHR Network Environment for Aboriginal Health Research (NEAHR)

Indigenous and Northern Affairs Canada

Canadian Circumpolar Institute

The communities of Aklavik, Old Crow, Fort McPherson and Tuktoyaktuk
Questions???

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