Research Update

H. pylori Infection in the Northwest Territories

CANHelp (Canadian North Helicobacter pylori) Working Group

Northern Health Services Network
Northwest Territories Health and Social Services
University of Alberta
Helicobacter in the Northwest Territories: the Aklavik project

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For the Aklavik Project Team
Thanks to John from Axcan Pharma for lunch
Aklavik *H. pylori* Project

**Timeline**

- **Wave 1**
  - *H. pylori* breath tests: Jan - Feb 2008
  - Scope week: Feb 4-8, 2008
  - Histopathology assessment: Feb – Apr 2008
  - Microbiology, culture & susceptibility: Feb – Sep 2008
  - Pathology results reported to participants: Apr 2008
  - Epidemiology survey, initial phase: Apr 2008
- **Wave 2**
  - New enrolment campaign: Sep-Oct 2008
  - Breath tests, surveys: Sep-Oct 2008
- **Treatment**: Oct-Nov 2008
- Long-term treatment follow-up: through Dec 2009
- Inform community of research results: Ongoing
Aklavik *H. pylori* Project Participation (Fall 08)

- Participants recruited: **314**
- Clinical surveys completed: **314**
- Individuals with breath test results: **255**
- Aklavik residents appearing for endoscopy: **197**
- Individuals from whom biopsies were obtained: **193**
- Epidemiology surveys completed to date
  - Household: **74**
  - Individual: **119**
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Prevalence (Fall 08)

- Proportion positive on breath test:
  - 57% (145/255)

- 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%

- Atrophic changes 14%

- Intestinal metaplasia 16%

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<tr>
<th>Hp density</th>
<th>Percentage</th>
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<tr>
<td>3+</td>
<td>36%</td>
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<tr>
<td>2+</td>
<td>37%</td>
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<tr>
<td>1+</td>
<td>27%</td>
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Gastritis much more severe than seen in Edmonton
Hp Resistance Aklavik

- 33% Metronidazole resistance
- 13% Clarithromycin Resistance
- 4% both C and M
Aklavik *H. pylori* Project

- Where are we going – what to do with the info from phase II...?
  - Phase III - Treatment
Treatment Phase

Aklavik H. pylori Project
Aklavik *H. pylori* Project

Treatment Considerations

- *H. pylori* infection is difficult to eliminate with currently available antibiotics, and the most effective regimens at present combine 2-3 antibiotics with an acid-suppressing drug.
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)

CM  69 %
OCM 87 %  GAIN 18%
CA  26 %
OCA 94 %  GAIN 68%

Gastroenterology 1999;116:248-253
Twice daily PPI triple therapy

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

are equally effective $\geq 70\%-80\%$
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Treatment Considerations

- A few anti-*H. pylori* treatment regimens somewhat higher success rates in trial reports.

1) **Quadruple therapy**,
   - proton pump inhibitor, bismuth, metronidazole and tetracycline

   Estimated to be 87% in Canada.

2) **10-day sequential therapy**
   - proton pump inhibitor and amoxicillin for days 1-5,
   - proton pump inhibitor in combination with tinidazole and clarithromycin days 6-10
RCT Sequential vs PPI-CA

- N = 300
- Results
  - Sequential 89%
  - PPI-CA 77%

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<tr>
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<th>Sequential</th>
<th>PPI-CA</th>
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<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>
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Ann Intern Med 2007;556-563
Aklavik *H. pylori* Project

**Treatment Considerations**

- Rationale for sequential therapy (De Francesco et al 2006).
  - amoxicillin, beta-lactam antibiotic,
  - compromises the cell wall
  - preventing efflux channel development for drugs like clarithromycin, making them more potent in phase two of the therapeutic regimen
What is the impact of resistance?

- clarithromycin-resistant strains
  - decreased effectiveness in treating with clarithromycin based regiments
- metronidazole-resistant strains
  - high-prevalence populations,
  - Can use metronidazole - higher dose and/or if the regimen is taken for a longer duration.
Objectives: Treatment Phase

1. Identify the most effective *H. pylori* therapy for infected individuals in the Aklavik *H. pylori* Project
2. Examine the effect of adherence to medication regimens and other clinical and demographic factors on treatment success
Participants: Treatment Phase

Positive UBT and/or biopsy-based evidence of *H. pylori* infection (pathology or culture)

Subdivided based on their *H. pylori* resistance profiles and previous therapeutic intervention:

1) Treatment naïve:
   - Metronidazole resistant
   - Clarithromycin resistant
   - Susceptible to all drugs assessed
   - No resistance profile available

2) Treatment failures
Inclusion Criteria

≥ 15 years old

evidence of *H. pylori* infection from initial study:
*breath-test positive,
histopathology or culture consistent with *H. pylori* infection

*Those without a breath test result at the outset of the trial will be required to complete one before enrolment. Those with inconsistent test results, will be offered the opportunity to repeat the breath test before deciding whether to undergo treatment, a decision that will be made in consultation with project physicians.*
Exclusion Criteria

Allergies to study medications
Treatment within the past 4 weeks with antibiotics
Severe cardio-respiratory, pulmonary, endocrine, hepatic or renal disease on anticoagulant therapy or other medication with serious drug interaction with study medications
Pregnant or lactating females
Subject Requirements

- Pre-treatment C13-urea breath test (if there is no baseline breath test available from earlier phases of this study.)
- Measure adherence (bubble pack round-up)
- Post treatment questionnaire
- Follow-up breath-test at 6-8 weeks post-treatment – to determine the outcome of treatment
- Re-treatment option for participants who fail to eradicate
Randomization

- Random number allocation
- If metro-R or without profile -> PPIAC vs ST
- If clari-R -> ST vs Q T

- Odd HP pack or QT (depending on their group allocation)
- Even to ST
RX for Aklavik H pylori Project: Phase III, Treatment

Patient: __________________________________________

DOB: __________________________________________

Healthcare number: ______________________________

PLEASE BLISTER PACK MEDICATIONS.

MEDS TO BE DISTRIBUTED TO THE SUSIE HUSKY HEALTH CENTRE: Aklavik NT

Rx (circled regimen is regimen prescribed):

a) Conventional therapy – PPI- AC :
   Rabeprazole 20mg po bid x 10/7
   Amoxicillin 1 gram po bid x 10/7
   Clarithromycin 500mg po bid x 10/7

b) Sequential therapy
   Rabeprazole 20mg po bid x 10/7
   Amoxicillin 1 gram po bid x 5/7 (days 1-5)
   Clarithromycin 500mg po bid x 5/7 (days 5-10)
   Metronidazole 500mg po bid x 5/7 (days 5-10)

c) Quadruple therapy
   Rabeprazole 20mg po bid x 10/7
   Bismuth 2 tablets qid x 10/7
   Tetracyclin 500mg po qid x 10/7
   Metronidazole 500mg po qid x 10/7

Repeats 0 (zero).

Dr Amy Morse R4 for Dr S van Zanten (Division of GI University of Alberta)
Results

- **53** Rx for PPI AC
- 3 Rx for Quadruple therapy
- **55** Rx for ST

- 74 (74/111 = 67%) packs returned thus far (as of Dec 28/08)

- 1 participant withdrawn for need for antibiotics for dental infection after treatment initiated
What’s next

• Follow-up U BT in Feb 09
• Questionnaire results pending
• Other communities...?
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
The Aklavik Project Team