Clinical Management of *H. pylori* Infection for Indigenous and Northern Communities in Canada: Guidelines Developed from CAN*Help* Research

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Community *H. pylori* (*Hp*) projects conducted by the CAN*Help* Working Group[1] during 2007-2018 generated local evidence of relevance to clinical decision-making about *Hp* infection in Arctic Indigenous communities. We used this information to adapt current Canadian guidelines for northern and Indigenous populations in Canada. Following the guidelines, we present the context and rationale for their development. ***Because evidence is limited for many of the recommendations we present, due weight should be given to the individual patient's motivation, values, preferences, and circumstances.***

Guidelines for Adults in Indigenous and Northern communities in Canada

- Locally relevant cost-benefit estimates for gastric cancer prevention strategies aimed at screening for *Hp* infection and treating those who are positive are not available; however:
  - There is evidence of an increased gastric cancer risk in Arctic and Indigenous populations, along with evidence that curing *Hp* infection reduces gastric cancer risk
  - It is ethically imperative to convey this information to patients, while noting there is no way to know whether a specific *Hp*-positive person will get gastric cancer if not treated or be protected from getting gastric cancer if treated
- The following patients may benefit from testing for *Hp* and treating if positive
  - Those who worry about health risks from *Hp*
  - Those with a family history of *Hp,* peptic ulcer disease, or gastric cancer
  - Those with symptoms of dyspepsia (except if GERD symptoms, such as heartburn and/or regurgitation, dominate)
- Testing for *Hp* infection should not be ordered without a discussion with the patient that emphasizes the following:
  - Effective treatment to eliminate *Hp* infection requires taking multiple daily doses of 4 drugs for 14 days and returning for retesting to check whether the infection was cured
  - Patients should get tested for *Hp* infection only if they are prepared to commit to taking the treatment as prescribed
  - Antibiotic treatments taken incompletely can result in treatment failure and may select for resistant bacteria
- For patients with peptic ulcers confirmed by imaging:
  - Those with duodenal ulcers who are not referred for gastroscopy should be tested by UBT and treated if positive
  - Those with gastric ulcers should be advised to undergo gastroscopy because gastric ulcers can occur with gastric cancer
  - Patients should be informed that strong evidence shows that successful elimination of *Hp* infection helps cure ulcers, prevents their recurrence, and improves ulcer-associated symptoms
- Patients seeking care for dyspepsia symptoms should be referred for gastroscopy if the following conditions apply:
    - ≥50 with new onset of symptoms
    - Little/no symptom improvement with acid suppression treatment
    - Alarm symptoms: **V**omiting; **B**leeding/anemia; **A**bdominal mass or unexplained weight loss; **D**ysphagia

- For patients referred for gastroscopy, if gastric biopsies show intestinal metaplasia or severe atrophy, the option of endoscopic surveillance should be considered and discussed with those who have other gastric cancer risk factors, ***especially if the intestinal metaplasia is extensive (in both gastric antrum and body) or more than mild***;[2] other gastric cancer risk factors include:
  - Indigenous ethnicity
  - Immigration from a high incidence region
  - Family history of gastric cancer in 1st degree relative, especially if onset age was early
  - Smoking
- For patients seeking care for dyspepsia symptoms (except if GERD symptoms dominate) who are under 50 and have no indications for gastroscopy, the following considerations should be conveyed to help them make an informed choice regarding options:
  - They should avoid known risk factors for dyspepsia (NSAID/ASA use, smoking, excessive alcohol use, and dietary factors such as high fat meals) to the extent possible to see if symptoms improve
  - Clinical studies show that successful treatment of *Hp* infection in people with dyspepsia can lead to improvement of symptoms; it should be emphasized, however, that some patients will have ongoing dyspepsia symptoms despite cure of *Hp*
  - Although *Hp* infection may not be the cause of their abdominal symptoms, *Hp* infection may increase the risk of stomach cancer, and for this reason, they may wish to get tested and take treatment if they test positive
- Recommended therapies (Table 1) should be prescribed for 14 days[3]
- If therapy fails, a different regimen should be offered; there is no point to using the same treatment twice unless the patient did not adhere to the regimen adequately
- A reasonable approach for treatment of *Hp* infection is to give up to 3 consecutive rounds of therapy, using a different regimen each time a post-treatment test shows treatment failure (for example: 1st ClaMET, 2nd Bismuth Quad, 3rd Levofloxacin-based); if the 3rd round fails, refer to a gastroenterologist and consider gastroscopy
- Whenever treatment to eliminate *Hp* infection is offered, treatment success should be confirmed with follow-up UBT (or *Hp* stool antigen test or, if indicated, gastroscopy); retesting should be done at least ***4 weeks after treatment is completed***

Differentiating Adolescents from Adults

According to a Canadian Paediatric Society position statement:[4] "Adolescence begins with the onset of physiologically normal puberty, and ends when an adult identity and behaviour are accepted…roughly…between…the ages of 10 and 19 years. Those responsible for providing healthcare to adolescents must allow…flexibility in this age span to encompass special situations such as [early emancipation,]…delayed development or prolonged dependency." It should be noted that there is ***no evidence to guide the identification of the age at which adolescents should be treated as adults with respect to testing for Hp*** and offering treatment if positive. For adolescents, a decision should be made in consultation with the patient (and/or parents) regarding the suitability of options available to adults under 50.

Table 1. Recommended Regimens for Eliminating *Hp* Infection[3]

Regimen, *Duration*	Medications (dose)	Total pills/day
First line (for treatment-naïve patients)		
Clarithromycin-based Quadruple, *14 days* (Also called: Concomitant, ClAMET)	Proton Pump Inhibitor (1 tablet, 2x/day) Clarithromycin (500 mg, 2x/day) Amoxicillin (1000 mg, 2x/day) Metronidazole or Tinidazole (500 mg, 2x/day)	8
Bismuth-based Quadruple, *14 days*	Proton Pump Inhibitor (1 tablet, 2x/day) Bismuth subsalicylate {Pepto Bismol®} (2 tablets, 4x/day) Metronidazole or Tinidazole (250-500 mg, 4x/day) Tetracycline (500 mg, 4x/day)	14
Rescue (prior treatment failure) – *avoid previously failed regimens*		
Bismuth-based Quadruple, *14 days*	*As above*	14
Clarithromycin-based Quadruple, *14 days*	*As above*	8
Levofloxacin-based, *14 days*	Proton Pump Inhibitor (2) Amoxicillin (1000 mg, 2x/day) Levofloxacin (250-500 mg, 2x/day)	5-6
Rifabutin-based, *10 days (Only for ≥3 prior treatment failures)*	Proton Pump Inhibitor (1 tablet, 2x/day) Amoxicillin (1000 mg, 2x/day) Rifabutin (150 mg, 2x/day)	6

Guidelines for Children[5]

- Current evidence suggests ***Hp* infection does not cause symptoms in children in the absence of peptic ulcer disease** (PUD)
- **Non-invasive testing for *Hp* is not recommended for children**, in general, or for children with functional abdominal pain without alarm signs, in particular
- Endoscopy is not indicated for children with functional abdominal pain without alarm signs
- Children with alarm signs (persistent significant abdominal pain, dysphagia, odynophagia, persistent vomiting, gastrointestinal blood loss, involuntary weight loss, deceleration of linear growth, delayed puberty, unexplained fever, or family history of inflammatory bowel disease, celiac disease, or PUD) should be referred for specialist care
- Children with gastric or duodenal ulcers should be tested for *Hp* (as part of endoscopic investigation) and offered treatment if positive
  - Patients (and/or parents) should be told that strong evidence shows that successful elimination of *Hp* infection helps cure ulcers and prevents recurrence of ulcers
- Children with iron-deficiency anemia (IDA) refractory to iron therapy when other causes have been ruled out should be referred for specialist care; such children should be tested for *Hp* as part of endoscopic investigation and offered treatment if positive
- Testing for *Hp* is not recommended for the initial investigation of IDA or for short stature

- If *Hp* is an incidental finding on biopsies taken during endoscopy, a treatment decision should be based on discussion with patients (and/or parents) to emphasize the following:
  - *Hp* infection is not likely to be the cause of the symptoms, so *Hp* treatment should not be expected to cure the symptoms
  - Potential benefits of treatment: reduced risk of PUD and gastric cancer later in life
  - Potential risks of treatment: treatment failure and the need for repeat treatment; adverse effects of antibiotics such as diarrhea or disruption of the gut microbiome
  - Young children (< 10 years) are at increased risk of reinfection
  - Treatment regimens require multiple daily doses of several drugs for 14 days
  - Incompletely taken treatments can select for resistant bacteria
  - If adherence is likely to be a challenge, treatment can be postponed until the child is older
- Dosing of *Hp* treatment in children is based on weight
- When *Hp* treatment is offered, practitioners should explain to the family the importance of adherence to the anti–*Hp* therapy for treatment success
- When *Hp* treatment is offered, treatment success should be confirmed by UBT or stool antigen test 4-6 weeks after treatment completion
- For therapy options see reference[5]

Background

Several updated guidelines pertaining to clinical management of *Helicobacter pylori* (*Hp*) infection in North America appeared in 2016-2018.[6,3,5,7–9] These updates arose in response to a globally recognized need to improve the effectiveness of clinical management strategies, including choice of treatment, for this infection. As pointed out by Graham and Fischbach in 2010:[10] "A decade ago it seemed that [*Hp*] treatments would soon…provide the same high level of treatment success demanded of other common infections. Unfortunately, that goal was not achieved and…the effectiveness of most commonly recommended treatments has declined to unacceptably low levels, largely related to development of resistance to clarithromycin…There are many reasons that successful treatment…of [*Hp*] infections remains a challenge…[including]…the nature of the organism…,the intragastric environment where the organism resides…,the regimens used to eradicate the organism…,and the behaviour and reactions of the host."[10]

This commentary proposed that "***Clinicians should use the rule 'only use what works locally' and…ignore consensus statements and society guidelines if the results are not consistent with local treatment results***." It stated further, "Because [*Hp*] is typically acquired in childhood, most patients have been infected for many decades and ***clinicians should feel no sense of urgency regarding initiating treatment***. Physicians should take whatever time is needed to gather the information needed for a successful result." [emphasis added][10]

The new guidelines share some new directions in the clinical management of *Hp* infection.

Greater caution for test and treat. Non-invasive testing and prescribing antimicrobial treatment without endoscopic assessment of gastric pathology should only be considered for adults under 50 with dyspepsia excluding alarm symptoms, or adult patients without dyspepsia who have a family history of gastric cancer.

Greater caution for the use of clarithromycin-based triple therapy. The formerly recommended clarithromycin-based triple therapy [Proton Pump Inhibitor (PPI), Clarithromycin (Cl) & Amoxicillin (A)] should not be used as a first-line regimen unless resistance to clarithromycin is known to be low (<15-20%) based on antimicrobial susceptibility testing, if available, or the local prevalence of resistant infection, if known, or lacking that, the patient's past exposure to clarithromycin. Where clarithromycin resistance is likely or treatment failure is common, quadruple therapy is preferred, either clarithromycin-based [PPI-Cl-A-Met], which has fewer pills/day, or bismuth-based [PPI, Bismuth, Met, and Tetracycline].

Increasing treatment duration to 14 days. Results of clinical trials show that treatment regimens prescribed for 14 days can overcome resistance and help prevent resistance from developing. The latter is particularly important where treatment failure is common.

Confirming treatment success. Using a noninvasive test after treatment to confirm elimination of the infection is crucial to identify patients who need another course of treatment (in which case, a different regimen should be used). Confirming treatment success routinely also provides local information on treatment effectiveness.

Engaging patients in making an informed choice. Patients should understand that *Hp* treatment does not always lead to symptom improvement and that treatment success depends on adhering to the regimen as prescribed. While successful antimicrobial treatment may reduce disease risks from *Hp* infection, therapy can have adverse effects that may make it difficult to complete treatment. Also, antimicrobial therapy may disrupt beneficial gut flora, and if taken incompletely, can contribute to antimicrobial resistance. A decision to test for *Hp* infection

should consider the patient's preferences with respect to pros and cons of treatment, and prospects for tolerating and adhering to a complex treatment regimen; the decision should also consider characteristics relevant to potential benefits of treatment, such as family history of *Hp* infection, peptic ulcer disease and gastric cancer.

While it should be noted that the 2016 Canadian guidelines for clinical management of *Hp* infection were developed primarily for settings where *Hp* prevalence is low, a good adaptation of these guidelines comes from Toward Optimized Practice (topalbertadoctors.org),[11] which aims to help Alberta practitioners implement evidence-based practices to optimize patient care. The Toward Optimized Practice Clinical Practice Guideline for Diagnosis and Treatment of *Hp* Infection in Adults (excluding pregnant/breastfeeding women) provides the recommendations listed below for patients seeking care for symptomatic dyspepsia (see also[12,13]). These guidelines, currently undergoing updating, will also suggest that testing for *Hp* infection by UBT, or stool antigen test, and offering treatment if positive be considered for patients without dyspepsia who have a family history of gastric cancer in a first degree relative.

Management of adult patients seeking care for symptoms of dyspepsia[11,12]

- **Adults of all ages** with the following should be referred for gastroscopy
  - Alarm symptoms
    - **V**omiting, **B**leeding/anemia, **A**bdominal mass or unexplained weight loss, **D**ysphagia
  - Diagnosed gastric ulcers (to exclude the risk of gastric cancer)
  - Little/no symptom improvement with acid suppression treatment
- **Adults ≥50** with the new onset of dyspepsia symptoms (excluding dominant symptoms of heartburn and/or regurgitation suggesting GERD[14]) should be referred for endoscopy
- For **Adult patients >50** without alarm symptoms
  - Suggest reducing exposure to known risk factors for dyspepsia (NSAID/ASA use, smoking and excessive alcohol use, and dietary factors such as high fat meals)
  - Consider testing for *H. pylori* infection by UBT and offer treatment if positive
  - For treatment regimens, the 2016 Canadian guidelines[3] or the Alberta Clinical Practice Guidelines[11] should be followed
- Patients with duodenal ulcers confirmed by imaging who are not referred for gastroscopy should be tested for *Hp* by UBT and treated if positive

Information Used for Adapting Alberta Guidelines for Indigenous and Northern Communities in Canada

We used data generated by community *Hp* projects conducted by the CAN*Help* Working Group,[1] which screened participants for *Hp* by UBT and offered upper GI endoscopy with gastric biopsy for pathological assessment. While these projects were restricted to communities in Yukon and the Beaufort-Delta of the Northwest Territories, many findings are similar to observations from other Indigenous communities in Canada and Alaska,[15] and other regions of the world where *Hp* prevalence and gastric cancer rates are high.

CAN*Help* Project Participation and Disease Burden Descriptions

- Despite efforts to accommodate all community members who wished to be screened for *Hp*, the proportion screened varied widely; in 8 communities with populations <1000:
  - Screening participation ranged roughly from 10-80%, averaging 33%
- Across communities, 59% of screened Indigenous participants tested *Hp*-positive
- Frequencies of chronic digestive symptoms reported by participants did not differ notably by *Hp* status (adjusting for age, sex, ethnicity, PPI or acid suppressor use, NSAID use, smoking and alcohol intake), with roughly half in either group reporting no symptoms
- Factors associated with reporting one or more chronic dyspepsia symptoms (excluding heartburn and reflux) were: older age; female sex; NSAID use; smoking and alcohol intake
- *Hp* infection occurred with gastric pathology indicative of increased gastric cancer risk (severe chronic gastritis, atrophic gastritis, and intestinal metaplasia) more frequently in project participants than in a comparison population of U of A Hospital patients[16]

Furthermore, cancer registry data show:

- Increased gastric cancer incidence rates in
  - Indigenous residents of the Northwest Territories relative to Canada as a whole[17]
  - Indigenous Albertans relative to non-Indigenous Albertans[18]
  - Indigenous populations relative to non-Indigenous counterparts worldwide[19]
- Gastric cancer is the 4th most frequent site for cancer mortality in Yukon men and 5th in Yukon women,[20] in contrast to 10th in men and women across Canada[21]
- 48% of gastric cancer cases diagnosed in the Northwest Territories during 1997-2015 occurred in people under 60 (as well as >40% of gastric cancer cases diagnosed in Yukon, versus <25% across Canada as a whole, during similar time periods)[17]
- 16% of gastric cancer cases diagnosed in Indigenous residents of the Northwest Territories during 1997-2015 occurred in people under 40 (versus <2% across Canada as a whole)[17]

CAN*Help* Project Treatment Trial Participation and Effectiveness Results:

- Of 682 participants who tested positive for *Hp* by UBT, 31% did not accept the offer of treatment; this proportion ranged across communities roughly from 20-40%
- Two quadruple (4-drug) regimens evaluated had estimated effectiveness over 90%
- Classic triple therapy (PPI, Clarithromycin, Amoxicillin) was inferior to quadruple therapies
- Adherence to treatment was excellent among participants who returned for follow-up testing
- Of 473 participants to whom treatment was dispensed, 35% did not return for follow-up testing (and we don't know if they completed treatment)
- Among 83 participants who were retested an average of 2.9 years after successful treatment, 71 (86%; 95% CI, 76-92%) remained free of *Hp* infection
- In a small group of participants who had a second endoscopy a few years after the first, most of those successfully treated showed improvement in gastric pathology while most of those whose infection was not eliminated did not show improvement in gastric pathology[22]

The participation rates reveal a challenge for initiatives aimed at preventing gastric cancer by eliminating *Hp* infection. While mounting evidence from other countries suggests that screening for *Hp* and treating those who test positive is cost-effective for preventing gastric cancer and peptic ulcer disease, this evidence so far pertains primarily to large trials conducted in East Asian countries. In 2014, a working group sponsored by the International Agency for Research on

Cancer assessed this evidence,[23] concluding that the evidence was insufficient with respect to details (who to target, how to test, how to treat) that would make such a strategy cost-effective, noting that such details will vary from one country to another. The report called for countries to generate their own evidence to build gastric cancer prevention strategies. Current European clinical guidelines recommend surveillance of gastric pre-cancerous lesions (intestinal metaplasia or severe atrophy) detected during gastroscopy among patients with gastric cancer risk factors including Indigenous ethnicity, immigration from a high incidence region, family history of gastric cancer, or intestinal metaplasia that is extensive (that is, in both antral and body biopsies) or of incomplete cell type.[2]

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