OBJECTIVE

Alberta clinicians will understand the indications to test for *Helicobactor pylori* (*H. pylori*), different testing methods available (urea breath test [UBT], histology on gastroscopy, stool tests), and the different treatment regimens available.

TARGET POPULATION

Adults meeting specific clinical criteria (see Indications)

EXCLUSIONS

Pregnant or breastfeeding women

Children (under 18 years of age)

RECOMMENDATIONS

INDICATIONS

- ✓ Testing for *H. pylori* can be performed with (non-invasive) Urea Breath Test (UBT) or (invasive) endoscopically guided biopsy. The UBT is the preferred approach for dyspeptic patients without alarm features.

See Algorithm (summarizing diagnosis and treatment process described below).

- ✓ Patients who would benefit from *H. pylori* testing using UBT include:
  - Dyspepsia and younger (< 50 years of age) with no alarm features
  - Gastric or duodenal ulcers confirmed by upper gastrointestinal (GI) radiography (if endoscopy not being considered)
  - Family history of gastric cancer
  - Long-term use of non-steroid anti-inflammatory agents (NSAIDS)

PRACTICE POINT

Patients with GERD predominant symptoms do not require UBT.

- ✓ Assess by endoscopy to exclude complicated disease and/or upper GI malignancy those patients with:
  - New onset persistent dyspepsia in patients > 50 years of age
  - No or limited response to acid-suppression treatment
  - Dyspepsia and any alarm features

PRACTICE POINT

When further assessment is required for dyspeptic patients, upper GI endoscopy is the preferred investigation. Barium swallow or CT scan can be ordered as a substitute if limited access to gastroscopy exists.

- Alarm Features can be recalled by the mnemonic **VBAD**.

• "**V**"omiting • "**B**"leeding or anemia • "**A**"bdominal mass or unexpected weight loss • "**D**"ysphagia

✓ Treat patients who test positive for *H* pylori infection.

DIAGNOSIS

X DO NOT use IgG serology test and stool antigen tests (SATs) for diagnosis of *H. pylori* infection.

✓ Refer to TOP's clinical practice guideline (CPG) for Diagnosis and Management of Gastroesophageal Reflux Disease (GERD) when symptoms are predominantly heartburn and/or acid regurgitation.

✓ Refer to TOP's CPG for Diagnosis and Treatment of Chronic Undiagnosed Dyspepsia in Adults for approach to patients with dyspepsia.

TREATMENT

See Table 1: Options for Treatment.

✓ Consider the efficacy, simplicity, expense and patient preferences when selecting treatment regimens.

PRACTICE POINT

If one eradication therapy fails, use a different regimen.

PRACTICE POINT

All treatment regimens should ideally be prescribed for 14 days but no less than seven days. There is an additional improvement of H. pylori *eradication of 1% per day if treatment continued beyond seven days.*

✓ Inform patient that no eradication protocol is 100% effective.

TREATMENT REGIMENS AVAILABLE

✓ Discuss treatment options with patient. Efficacy, complexity, cost, previous eradication therapies used and patient preferences should help guide choice of regimen.

- To compare medication costs for various treatment options see: https://www.acfp.ca/2016-price-comparison-of-commonly-prescribed-drugs-available/.

POSSIBLE *H. pylori* ERADICATION REGIMENS (PATIENTS NOT ALLERGIC TO PENICILLIN)		
Options for first line treatment	***Notes: Efficacy***	***Notes: Ease of use/cost***
CLAMET Quadruple Regimen x 14 days 1. PPI* (1 tablet) two times a day 2. Amoxicillin (1 g) two times a day 3. Clarithromycin (500 mg) two times a day 4. Metronidazole (500 mg) two times a day	Recommended first line therapy by Canadian expert consensus.[1] Potentially greater adverse events compared to other therapies.[2]	Less complicated and fewer tablets than other first line regimens.
Bismuth Quadruple Regimen x 14 days 1. PPI (1 tablet) two times a day 2. Bismuth subsalicylate (Pepto Bismol®) (2 tablets) four times a day 3. Metronidazole (500 mg) four times a day 4. Tetracycline (500 mg) four times a day	Recommended as alternate first line by Canadian expert consensus.[1]	More complicated and most tablets to be taken: 308 tablets.
Sequential Therapy x 14 days PPI bid 1-14 days Amoxicillin (1 g) two times a day for 1-7 days then Clarithromycin (500 mg) and Metronidazole (500 mg) two times a day 7-14 days	No longer recommended by Canadian expert consensus.[1]	
Standard Triple Therapy (PAC) x 14 days 1. PPI two times a day 2. Amoxicillin (1 g) two times a day 3. Clarithromycin (250 mg) two times a day or Metronidazole (500 mg) two times a day	No longer recommend by Canadian expert consensus.[1]	Easier regimen, option if local clarithromycin resistance is known to be <15% but current resistance rates throughout Alberta are not available at this time.
Second line treatment – **rescue therapy for failed first line**		
✓ Use an alternate first line therapy	See above.	See above.
Option for third line treatment – **if second line treatment failure (no amoxicillin allergy) and consider referral to Gastroenterology x 14 days**		
1. PPI (1 tablet) two times a day 2. Amoxicillin (1 g) two times a day 3. Levofloxacin (250 mg) two times a day	Only for failed second treatment Side effects	
TREATMENT OPTIONS (PENICILLIN ALLERGIC OPTIONS)		
First line treatment (Amoxicillin allergy)		
Bismuth Quadruple Regimen x 14 days 1. PPI (1 tablet) two times a day 2. Bismuth subsalicylate (Pepto Bismol®) (2 tablets) four times a day 3. Metronidazole (500 mg) four times a day 4. Tetracycline (500 mg) four times a day	Recommended expert consensus for first line (amoxicillin allergy). As above.	As above.
Modified Triple Therapy (PCM) x 14 days 1. Pantoprazole 40 mg two times a day 2. Clarithromycin (500 mg) two times a day 3. Metronidazole (500 mg) two times a day	Less effective than first line treatment	Less complicated (compared with other regimens) May be lower cost for patient.

Table 1: Options for Treatment **proton pump inhibitor (PPI)*

CONFIRMING ERADICATION

- ✓ Order UBT to confirm *H. pylori* eradication for:
  1. Patients whose symptoms remain or recur after treatment:
     - Do not treat *H. pylori* empirically without confirming that *H. pylori* is still present.
  2. Patients with *H. pylori* positive gastric or duodenal ulcer or gastric cancer (if endoscopy not being performed)

POST-THERAPY RE-TESTING WITH UBT

- ✓ Wait to re-test with UBT at least 28 days following any antibiotic use (including *H. pylori* eradication therapy).
  - Testing before 28 days may result in false negative results.
- ✓ Discontinue proton pump inhibitor (PPI) therapy for at least three days.
  - Recommend OTC antacids if needed to control symptoms.

Please see Dynalife/Calgary Lab Services (CLS) for instructions.

THE REPEAT UBT IS NEGATIVE (AND PATIENT IS STILL SYMPTOMATIC)

- ✓ Reconsider other potential causes of the symptoms.
  - For (non-ulcer) dyspepsia see TOP's Diagnosis and Treatment of Chronic Undiagnosed Dyspepsia in Adults CPG.

THE REPEAT UBT IS POSITIVE, H. pylori IS PRESENT AND ERADICATION THERAPY HAS FAILED

- ✓ Always use a different eradication regimen.
- ✓ Consider initial reason for *H. pylori* testing and a gastroenterologist referral to further assess (i.e., test *H. pylori* culture and sensitivity) after two or three unsuccessful treatment attempts.

BACKGROUND

EPIDEMIOLOGY

H. pylori infection is common in Canada, although decreasing because the incidence is low in children born in Canada. The prevalence increases with age,[3] varies by region and ethnic sub-groups ranging from about 20% to 40% in some adult populations.[4] The prevalence is high, often greater than 50%, in First Nations populations living in northern Canada.[5]

Although the source of *H. pylori* infection has not yet been found, it is likely transmitted from human to human in childhood.

Relationship Between H. pylori and Gastritis, Gastric/Duodenal Ulcers

It is estimated that 10% to 20% of *H. pylori*-positive patients will have a lifetime risk of developing ulcer disease and a 1% to 2% risk of developing distal gastric cancer.[6]

H. pylori infection may be associated with dyspepsia symptoms but treating *H.pylori* doesn't always improve dyspepsia symptoms.[3] If symptoms persist despite successful cure of infection these patients may benefit from ongoing acid suppressive therapy. (See the section on empiric therapy in Diagnosis and Treatment of Chronic Undiagnosed Dyspepsia in Adults CPG.)

Aspirin® and NSAIDS are common causes of peptic ulcer disease. There is an increased risk of peptic ulcers if both *H. pylori* infection is present and NSAIDS or aspirin are used.[7] Therefore, patients contemplating or currently on long term NSAIDs should be considered for UBT and eradicating *H. pylori* if positive.[8]

Relationship Between H. pylori and Gastric Malignancy

H. pylori is associated with the development of gastric cancer. The lifetime risk of gastric cancer is about 2% for male and 1% for female Canadians.[9] A recent systematic review of randomized controlled studies found that in patients in which *H. pylori* was eradicated, the incidence of gastric cancer is reduced relatively by about 33%.[10] The absolute benefit depends on the population studied who would have differing baseline rates.

Other risk factors for gastric cancer include family history of gastric cancer and lifestyle factors such as smoking, drinking alcohol, and a diet low in fruits and vegetables or high in salted, smoked, or nitrate-preserved foods.[11]

Testing for H. pylori – Urea Breath Test

The urea breath test (UBT) is a simple non-invasive diagnostic test used to identify *H. pylori*.

Overall, performance characteristics of the UBT are superior to any other diagnostic test with sensitivity and specificity generally exceeding 95% in most reports[12-14] and test reproducibility is high.[15]

The UBT can also be used for post- treatment testing.[16-19] However, test sensitivity is decreased by medications (such as bismuth containing compounds, antibiotics, and PPIs) that reduce the organism's urease activity or density,[20] therefore a washout period is required. See respective lab services for washout instructions:

- Dynalife: http://www.dynalifedx.com/Portals/0/pdf/Patient%20instructions/Urea%20breath.pdf
- Calgary Lab Services: http://www.calgarylabservices.com/lab-services-guide/lab-tests/AlphabeticalListing/U/Urea-Breath-Test-For-Helicobacter-pylori.htm

Tests Not Recommended for H. pylori Detection

H. pylori antibody testing (IgG serology) detects antibodies to the bacteria but will not distinguish a previous infection from the current one (i.e., test would be positive if the patient ever had *H.pylori*) so additional testing would always be required). However, if the test result is negative, it is unlikely that a person ever had an *H. pylori* infection.

The *H. pylori* stool antigen test (SAT) was found to have a lower diagnostic value than UBT when evaluating the outcome of anti-*H. pylori* therapy. Temperature, consistency of stool, interval between stool sample collection and measurement of stool can also affect the results of SATs.[21] The use of SATs should only be considered if the UBT is not available.[22]

H. pylori Treatment

The standard triple therapy-proton pump inhibitor-clarithromycin/amoxicillin (PCA) has been the recommended approach to treat *H. pylori* with a high level of treatment success (>80% eradication) in Canada.[23] However, studies from other countries suggest there has been a steady worldwide decline in the success rate of triple therapy primarily due to clarithromycin resistance.[24,25] Unfortunately local resistance rates are not readily available in Alberta or Canada.

A meta-analysis of 17 Canadian trials reviewed the eradication success with differing treatments regimens:[23]

- Standard Triple therapy (PCA) 84% (79 to 90% range)
- Modified Triple therapy (PCM) 82% (76 to 88% range)
- Bismuth Quadruple Therapy 87% (80-95% range)

When patient adherence with prescribed regimen was >75%:

- Quadruple therapy about the same as triple therapy (91-94% range)

More recent unpublished tertiary care Alberta data found that triple therapy was only successful in 55% of patients.[26]

A randomized control trial (RCT) conducted in the North West Territories found 10 days of triple therapy or sequential therapy successfully eradicated *H. pylori* in only 55 and 57% of patients respectively. Of 77 participants with complete medication adherence, effectiveness improved to 63% (95% CI 43% to 82%) for triple therapy and 81% (95% CI 63% to 99%) for sequential therapy. This study was however limited by about 20% of patients lost to follow up (were considered to still be *H.* pylori positive). This would result in lower than anticipated eradication rates.[27]

See Table 2 for a more recent network meta-analysis of *H. pylori* eradication regimens data.[10,28]

Therapy and Duration	Eradication (average and range) %	Adverse Events (average and range) %
Triple therapy (PCA) 7 days	73% (71-75)	21% (18-26)
Triple therapy (PCA) 10-14 days	81% (78-84)	24% (18-29)
Sequential therapy 10 days	87% (85-90)	22% (17-27)
CLAMET Quadruple 7 days	94% (89-98)	26% (10-48)
Bismuth Quadruple 10-14 days	85% (82-89)	23% (17-30)

Table 2: H. pylori Eradication Regimens and Effects

From the meta-analysis described in Table 2, the CLAMET quadruple therapy was based on one low quality study of 119 Japanese patients where clarithromycin resistance is >20%, no studies could be located directly comparing 10 or 14 days to 7 days of Triple Therapy.

Recent Canadian guidelines no longer recommending triple or sequential therapy but recommend Clarithromycin, Amoxicillin, Metronidazole (CLAMET) quadruple regimen as first line therapy.[1]

Treatment Duration

Canadian guidelines recommend that all treatment durations for *H. pylori* be 14 days.[1]

Generally, for every day of therapy beyond seven days, an additional 1% of patients will be successfully eradicated.[29] This benefit must be balanced with potentially greater risk of adverse events, costs and risk of non-adherence.[29]

Patient non-adherence with treatment regimens increases chance of treatment failure. Patients must be informed that adherence with treatment regimen is critical to successful eradication to prevent antibiotic resistance. Patients must also understand that no eradication protocol is 100% effective and failure of treatment is possible.

Treatment Failure

First Failure: use an alternate therapy (do not repeat initial regimen). See Table 1.

Second failure: consider another alternative and referral to gastroenterologist.

Confirming Eradication with UBT

UBT is the best non-invasive test for the presence or absence of *H. pylori.*[20]

UBT testing for eradication of *H.pylori* should be considered for:

- Dyspeptic patients (without alarm features) who continue to be symptomatic after a full course of treatment to confirm either eradication of *H.pylori* or failure of treatment
- Dyspeptic patients who initially improve post eradication, but develop recurrent symptoms
- Patients treated for gastric or duodenal ulcer or gastric cancer to document cure of *H. pylori (*only if not considering gastroscopy). This will establish success of the anti-*Helicobacter* therapy regimen and in the case of gastric ulcer rule out any gastric cancer.[20]

UBT INSTRUCTIONS

It is necessary to have at least a 28-day wash-out period before re-testing with UBT following completion of any antibiotics (including *H. pylori* eradication therapy). Testing before 28 days may result in false negative results.

PPI therapy can also result in false negative UBT results (as high as 40%)[30] and therefore should be discontinued three days prior to UBT testing.

Antacids can be prescribed if needed to control symptoms should PPI be temporarily stopped.

See: Dynalife and Calgary Lab Services instructions.

If UBT is negative, but symptoms persist or recur, other causes must be considered.

If UBT is positive, *H. pylori* is present and first line eradication therapy has failed – use an alternative therapy for *H. pylori.* If subsequent treatment fails, consider the initial indication for *H. pylori* testing and consider a referral to a gastroenterology specialist.

CPG IMPLEMENTATION IN PRACTICE CONSIDERATIONS

- Primary care physicians can bookmark the link to the CPG or copy the tools within the CPG for easy access including the *H.pylori* treatment option tables, the algorithm for summary of the care process, and other tools such as the listing of drug costs for *H. pylori* treatment.
- Gastroenterologists and endoscopists can promote the use of the TOP *H. pylori* CPG among primary care physicians who may be unfamiliar with the approach for *H. pylori* assessment, diagnosis and treatment.

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GUIDELINE COMMITTEE

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ALGORITHM

DIAGNOSIS AND TREATMENT OF *HELICOBACTER pylori* IN ADULTS*

*Excluding pregnant or breastfeeding women