Name:	DOB:
PHN/ULI:	RHRN:
RefMD: Dr.	RefMD Fax:
RefDate:	Date Today: March 8, 2016

CONFIRMATION: **Referral Received**

TRIAGE CATEGORY: **Enhanced Primary Care Pathway**

REFERRAL STATUS: **CLOSED**

Refractory H. PYLORI

Dear Dr. ,

The above-named patient was referred to GI-CAT for further assessment of refractory *Helicobacter pylori* (Hp) infection of the stomach and relevant GI symptoms. Based on full review of your referral, it has been determined that **management of this patient within the Enhanced Primary Care Pathway is appropriate, without need for specialist consultation at this time.**

This clinical pathway has been developed by the Calgary Zone Primary Care Network in partnership with the Section of Gastroenterology and Alberta Health Services. These local guidelines are based on best available clinical evidence, and are practical in the primary care setting. This package includes:

1. Focused summary of Hp relevant to primary care
2. Summary of 2016 Canadian Association of Gastroenterology Guidelines for treatment of *Helicobacter pylori*
3. Review of your patient's Hp treatment history
4. Recommended next-round Hp treatment regimen
5. Checklist for your in-clinic followup of this patient

This referral is CLOSED.

If you would like to discuss this referral with a Gastroenterologist, call Specialist LINK, a dedicated GI phone consultation service, available 08:00-17:00 weekdays at 403-910-2551 or toll-free 1-855-387-3151.

If your patient completes the Enhanced Primary Care Pathway and remains symptomatic or if your patient's status or symptoms change, a new referral indicating 'completed care pathway' or 'new information' should be faxed to GI Central Access and Triage at 403-944-6540.

Thank you.

Kevin Rioux, MD PhD FRCPC
Medical Lead, GI Central Access and Triage
Section of Gastroenterology

Enhanced Primary Care Pathway: HELICOBACTER PYLORI

1. Focused summary of Hp relevant to primary care

Epidemiology. The overall prevalence of Hp in Canada is about 20-30%, but is considerably higher in First Nations communities and in immigrants from developing countries in South America, Africa, and Asia where prevalence can be 70-90%. Infection most commonly occurs during childhood, likely by fecal-oral route. The prevalence of antibiotic resistant strains of Hp is high in certain immigrant populations.

Symptoms. Many humans are asymptomatic carriers of Hp, but those who develop significant gastroduodenitis experience dyspepsia, which is post-prandial epigastric pain or bloating, nausea, belching, early satiety, or loss of appetite. Most studies suggest that Hp does not play a role in gastro-esophageal reflux disease, and patients are understandably disappointed when their GERD does not improve after eradication of co-incidental Hp colonization.

Complications. About 5-15% of patients with Hp will develop duodenal or gastric ulcers, but this is higher in patients who chronically use nonsteroidal anti-inflammatory drugs including low-dose aspirin (e.g. for long-term management of arthritis or other pain conditions). Hp increases the risk of gastric adenocarcinoma and MALT lymphoma but overall the absolute risk of this is very low, less than 1%.

Diagnosis. The urea breath test (UBT) is the most commonly used non-invasive test for Hp in Calgary. False positive results are rare, but false negatives may result from recent use of antibiotics or antisecretory drugs (PPI or H2RA). Patients should be off antibiotics for at least 4 weeks before the test. CLS suggests stopping PPIs 3 days before the test, but preferably this should be 2 weeks, and ideally 4 weeks, which may be difficult for some patients who become symptomatic off PPI. The UBT costs about $45 and takes about one hour for the patient to complete.

Who to Test. (1) Patients with relevant upper GI symptoms, and those (2) with a first-degree relative with gastric cancer, (3) starting long-term NSAIDs, (4) history of peptic ulcer disease or upper GI bleed especially if contemplating use of low dose aspirin. There is no clear evidence-based guideline in Canada for testing asymptomatic individuals based on country of birth or aboriginal status.

Treatment. In 2016, the Canadian Association of Gastroenterology made significant changes to guidelines for treating Hp. Due to increased antibiotic resistance, standard triple therapy regimens are no longer part of first-line treatment, being replaced by 14-day quadruple therapies, as detailed below. Although resistance of Hp to metronidazole, clarithromycin, and levofloxacin is increasingly common, amoxicillin and tetracycline remain quite reliably active against Hp. Even antibiotics that Hp is resistant to can be a part of successful therapies when used synergistically with at least two other antibiotics and for longer duration. According to local experience, gastroscopy to test antibiotic sensitivities in patients with apparent refractory Hp offers little specific guidance in choice of subsequent treatment.

Confirming Eradication. Patients should always be retested for Hp at least 4 weeks after treatment; retesting too soon risks a false negative test. Once eradicated, re-infection is unusual. Transmission to others is unlikely so it is not routinely recommended to test spouses or children of patients with Hp, unless they have pertinent symptoms.

Treatment Failure. This may indicate antibiotic resistance, but certainly intolerance or non-adherence to treatment regimen must be explored with the patient. Recurrence likely represents recrudescence of the original infection, prompting alternative antibiotic regimens.

2. Hp treatment regimens (Canadian Association of Gastroenterology 2016 Guidelines)

Triple therapy (PPI + clarithromycin + amoxicillin or metronidazole) is no longer recommended, as studies of Hp isolates in Canada suggest 25-30% are resistant to metronidazole and 15-20% are resistant to clarithromycin.

With the exception of the rifabutin-based regimen, **all treatments for Hp should be 14 days duration**.

First Round		
CLAMET Quad for 14 days • PPI standard dose BID • Clarithromycin 500mg BID • Amoxicillin 1000mg BID • Metronidazole 500mg BID	**OR**	BMT Quad for 14 days • PPI standard dose BID • Bismuth subsalicylate 524mg QID • Metronidazole 375mg QID • Tetracycline 500mg BID
Second Round		
• If CLAMET Quad was used as initial treatment, then use BMT Quad for second round • If BMT Quad was used as initial treatment, then use CLAMET Quad or consider Levo-Amox		
Third Round		
Levo-Amox for 14 days • PPI standard dose BID • Amoxicillin 1000mg BID • Levofloxacin 250 mg BID		
Fourth Round		
Rif-Amox for 10 days • PPI standard dose BID • Rifabutin 150mg BID • Amoxicillin 1000mg BID		This should only be considered after failure or intolerance of the above three regimens. **Rifabutin has rarely been associated with potentially serious myelotoxicity, that is, low white cell or platelet count.** The pros and cons of giving fourth-line therapy should be decided on a case-by-case basis.

Patient information sheets for each of these regimens are attached below and are available from your PCN website. These one-page information sheets list important additional information about specific Hp treatment regimens including side effects and warnings. Ideally this should be presented and discussed with your patient during an in-clinic visit.

The patient should be reminded of the **importance of completing the entire treatment exactly as prescribed**. For clarity and convenience, particularly with the Quad therapies, it may be helpful to **have the prescription bubble packed** which is free or a nominal charge at most pharmacies.

If patients have had problems tolerating antibiotics in the past, **administration of probiotics for the entire duration of Hp treatment may improve tolerability and/or improve eradication rates**, although this is a broad generalization and comes at added cost to the patient. If your patient wishes to try this, evidence supports the use of *Lactobacillus* species, *Sacharomyces boulardi*, or multi-species formulations.

3. Review of previously tried Hp treatment(s) for patient:

Date UBT positive	Twice daily PPI + listed antibiotics	Duration (days)	Correctly prescribed/dispensed?
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

A = amoxicillin, B = bismuth, C = clarithromycin, L = levofloxacin, M = metronidazole, T = tetracycline, R = rifabutin

4. Suggested subsequent Hp treatment for patient:

- ☐ 14 day PPI + clarithromycin + amoxicillin + metronidazole CLAMET
- ☐ 14 day PPI + bismuth subsalicylate + metronidazole + tetracycline BMT
- ☐ 14 day PPI + amoxicillin + levofloxacin Levo-Amox
- ☐ 10 day PPI + rifabutin + amoxicillin Rif-Amox

Attached is a one-page information sheet for your patient about this regimen

5. Checklist to guide your in-clinic review of this patient <u>after</u> treatment of Hp

- ☐ Recheck UBT (off antibiotics ≥4 weeks; off PPI ≥3 days but preferably ≥2 weeks)
- ☐ If UBT remains positive, use an alternative treatment and recheck UBT. Refer to above treatment guidelines. If questions, please call GI Specialist Link at 403-910-2551 or toll-free 1-855-387-3151.
- ☐ If UBT negative but persistent symptoms, send in a <u>new referral</u> with full details to GI CAT re: diagnostic endoscopy.
- ☐ If UBT negative but family history of gastric cancer in a first-degree relative, send in a <u>new referral</u> re: screening endoscopy

PATIENT INFORMATION SHEET

CLAMET based quadruple therapy for *Helicobacter pylori* infection of the stomach

Take the following 4 medications for 14 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Clarithromycin 500mg	1 capsules (500mg)	2x daily
Amoxicillin 500mg	2 capsules (1000mg)	2x daily
Metronidazole 500mg	1 tablet (500mg)	2x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $160** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments.

Clarithromycin (Biaxin®): This antibiotic is frequently used to treat lung and ear infections, but is also effective against *H. pylori*. The most common side effects are taste disturbance (10%), loose stools (5%) and nausea (2%).

Amoxicillin (generic): This drug is commonly used to treat lung and bladder infections, but remains one of the most reliable antibiotics against *H. pylori*. The most common side effects are loose stools (7%) and skin rash (2%). Should a skin rash develop while on this medication, discontinue it immediately and contact your physician. If you have had an adverse reaction to penicillin at any time in the past, you must discuss the nature and severity of the reaction with your doctor to decide about the use of this medication.

Metronidazole (Flagyl®): This antibiotic is used to treat a variety of gastrointestinal infections. The most common side effects are nausea, metallic taste in the mouth and loose stools. It can interact with alcohol to produce flushing, nausea, low blood pressure, heart palpitations or chest discomfort and, therefore, you must not drink any alcohol while taking this drug.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of four drugs without too much difficulty.

Specialist *LINK* | Primary Care Networks Calgary and Area | Calgary Division of Gastroenterology & Hepatology | Alberta Health Services

PATIENT INFORMATION SHEET

BMT based quadruple therapy for *Helicobacter pylori* infection of the stomach

Take the following 4 medications for 14 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Bismuth subsalicylate (Pepto-Bismol®) 262mg	2 caplets (524mg)	4x daily
Metronidazole 250mg	1½ tablets (375mg)	4x daily
Tetracycline 500mg	1 capsule (500mg)	4x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $95** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments.

Bismuth subsalicylate (Pepto-Bismol®): This is an over-the-counter drug commonly used to treat indigestion, which also has antibiotic effects on *H. pylori*. Pepto-Bismol will cause dark coloring of the stool and/or black appearance of the tongue, which disappear after the medication is stopped. Nervous system side effects (i.e. dizziness and confusion) have been reported but are rare. Patients with kidney problems are at higher risk of these side effects and should consult their physician before taking this medication.

Metronidazole (Flagyl®): This antibiotic is used to treat a variety of gut infections. The most common side effects are nausea, metallic taste in the mouth and loose stools. It can interact with alcohol to produce flushing, nausea, low blood pressure, heart palpitations or chest discomfort and, therefore, you must not drink any alcohol while taking this drug.

Tetracycline (generic): This medication is commonly used to treat lung and skin infections, but also has reliable antibiotic effects on *H. pylori*. Side effects occur in less than 5% of patients and include nausea, vomiting, loose stools, and skin rash. Tetracycline sensitizes the skin to the harmful effects of ultraviolet light and, therefore, you must avoid prolonged sun exposure while on this medication.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of four drugs without too much difficulty.

Specialist LINK | Primary Care Networks Calgary and Area | Calgary Division of Gastroenterology & Hepatology | Alberta Health Services

PATIENT INFORMATION SHEET

Levo-Amox based triple therapy for *Helicobacter pylori* infection of the stomach

Take the following 3 medications for 14 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Levofloxacin 250mg	1 tablet (250mg)	2x daily
Amoxicillin 500mg	2 capsules (1000mg)	2x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $110** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments

Levofloxacin (Levaquin®): This antibiotic is most commonly used to treat lung, bladder, sinus, and skin infections, but is also used to treat *H. pylori* after initial failed attempts. It is generally well tolerated. The most common and minor side effects are headache, nausea, and diarrhea. Rare side effects include numbness or tingling in the hands or feet and liver inflammation or jaundice. Additional caution should be used in patients with known liver or kidney problems and in patients with heart rhythm problems. Very rarely, use of this medication has been associated with muscle tendon rupture. Levofloxacin should not be used by patients known to be allergic to antibiotics in the same drug class as ciprofloxacin.

Amoxicillin (generic): This drug is commonly used to treat lung and bladder infections, but remains one of the most reliable antibiotics against *H. pylori*. The most common side effects are loose stools (7%) and skin rash (2%). Should a skin rash develop while on this medication, discontinue it immediately and contact your physician. If you have had an adverse reaction to penicillin at any time in the past, you must discuss the nature and severity of the reaction with your doctor to decide about the use of this medication.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of three drugs without too much difficulty.

PATIENT INFORMATION SHEET

Rif-Amox based triple therapy for *Helicobacter pylori* infection of the stomach

Take the following 3 medications for 10 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription. This regimen is reserved for patients with *H. pylori* infection that persists despite multiple previous attempts at cure with distinct antibiotic combinations.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Rifabutin 150mg	1 tablet (150mg)	2x daily
Amoxicillin 500mg	2 capsules (1000mg)	2x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $170** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments.

Rifabutin (Mycobutin®): This antibiotic is usually used to treat tuberculosis, but is also very effective against *H. pylori* due to low prevalence of resistance. Rifabutin is expensive and may take a few days to obtain by your pharmacy. It commonly causes a metallic taste and orange-red discolouration of the urine. About 30% of patients experience headache, nausea, diarrhea, rash, or muscle/joint pain. Rare but potentially serious side effects (<2% incidence) include liver injury or dysfunction, or impairment of bone marrow production of blood cells with risk of fever, infection, or bleeding. In most cases, these rare adverse effects disappear when rifabutin is discontinued, but there a few reports of severe or persistent liver or bone marrow injury.

Amoxicillin (generic): This drug is commonly used to treat lung and bladder infections, but remains one of the most reliable antibiotics against *H. pylori*. The most common side effects are loose stools (7%) and skin rash (2%). Should a skin rash develop while on this medication, discontinue it immediately and contact your physician. If you have had an adverse reaction to penicillin at any time in the past, you must discuss the nature and severity of the reaction with your doctor to decide about the use of this medication.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of three drugs without too much difficulty.

Alberta Health Services

Gastroenterology CENTRAL ACCESS AND TRIAGE
Fax: 403-944-6540
http://www.calgarygi.com

Name:	DOB:
PHN/ULI:	RHRN:
RefMD: Dr.	RefMD Fax:
RefDate:	Date Today: March 8, 2016

IMPORTANT NOTICE

Closed GI Referral: *Helicobacter pylori* and relevant GI symptoms

Dear Dr. ,

The above-named patient was referred to GI Central Access and Triage (CAT) with upper GI symptoms and a positive urea breath test (UBT). You have already begun treatment for *Helicobacter pylori* (Hp), which may resolve the issue and obviate the need for GI consultation. The following is an appropriate course of action:

☐ Recheck UBT (off antibiotics ≥4 weeks; off PPI ≥3 days but preferably ≥2 weeks)
☐ If UBT remains positive, use an alternative treatment and repeat UBT. Please refer to attached summary of 2016 Hp treatment guidelines and patient information sheets for each of these regimens to guide your in-office discussion of subsequent treatment. If questions, please call GI Specialist Link at 403-910-2551 or toll-free 1-855-387-3151.
☐ If UBT negative but persistent symptoms, send in a new referral with full details to GI CAT re: diagnostic endoscopy.
☐ If UBT negative but family history of gastric cancer in a first-degree relative, send in a new referral re: screening endoscopy

This referral is CLOSED.

If you have any questions or concerns about this closed referral, please contact us via fax at 403-944-6540.

Thank you.

Kevin Rioux, MD PhD FRCPC
Medical Lead, Central Access and Triage
Section of Gastroenterology

1. Focused summary of Hp relevant to primary care

Epidemiology. The overall prevalence of Hp in Canada is about 20-30%, but is considerably higher in First Nations communities and in immigrants from developing countries in South America, Africa, and Asia where prevalence can be 70-90%. Infection most commonly occurs during childhood, likely by fecal-oral route. The prevalence of antibiotic resistant strains of Hp is high in certain immigrant populations.

Symptoms. Many humans are asymptomatic carriers of Hp, but those who develop significant gastroduodenitis experience dyspepsia, which is post-prandial epigastric pain or bloating, nausea, belching, early satiety, or loss of appetite. Most studies suggest that Hp does not play a role in gastro-esophageal reflux disease, and patients are understandably disappointed when their GERD does not improve after eradication of co-incidental Hp colonization.

Complications. About 5-15% of patients with Hp will develop duodenal or gastric ulcers, but this is higher in patients who chronically use nonsteroidal anti-inflammatory drugs including low-dose aspirin (e.g. for long-term management of arthritis or other pain conditions). Hp increases the risk of gastric adenocarcinoma and MALT lymphoma but overall the absolute risk of this is very low, less than 1%.

Diagnosis. The urea breath test (UBT) is the most commonly used non-invasive test for Hp in Calgary. False positive results are rare, but false negatives may result from recent use of antibiotics or antisecretory drugs (PPI or H2RA). Patients should be off antibiotics for at least 4 weeks before the test. CLS suggests stopping PPIs 3 days before the test, but preferably this should be 2 weeks, and ideally 4 weeks, which may be difficult for some patients who become symptomatic off PPI. The UBT costs about $45 and takes about one hour for the patient to complete.

Who to Test. (1) Patients with relevant upper GI symptoms, and those (2) with a first-degree relative with gastric cancer, (3) starting long-term NSAIDs, (4) history of peptic ulcer disease or upper GI bleed especially if contemplating use of low dose aspirin. There is no clear evidence-based guideline in Canada for testing asymptomatic individuals based on country of birth or aboriginal status.

Treatment. In 2016, the Canadian Association of Gastroenterology made significant changes to guidelines for treating Hp. Due to increased antibiotic resistance, standard triple therapy regimens are no longer part of first-line treatment, being replaced by 14-day quadruple therapies, as detailed below. Although resistance of Hp to metronidazole, clarithromycin, and levofloxacin is increasingly common, amoxicillin and tetracycline remain quite reliably active against Hp. Even antibiotics that Hp is resistant to can be a part of successful therapies when used synergistically with at least two other antibiotics and for longer duration. According to local experience, gastroscopy to test antibiotic sensitivities in patients with apparent refractory Hp offers little specific guidance in choice of subsequent treatment.

Confirming Eradication. Patients should always be retested for Hp at least 4 weeks after treatment; retesting too soon risks a false negative test. Once eradicated, re-infection is unusual. Transmission to others is unlikely so it is not routinely recommended to test spouses or children of patients with Hp, unless they have pertinent symptoms.

Treatment Failure. This may indicate antibiotic resistance, but certainly intolerance or non-adherence to treatment regimen must be explored with the patient. Recurrence likely represents recrudescence of the original infection, prompting alternative antibiotic regimens.

Hp treatment regimens (Canadian Association of Gastroenterology 2016 Guidelines)

Triple therapy (PPI + clarithromycin + amoxicillin or metronidazole) is no longer recommended, as studies of Hp isolates in Canada suggest 25-30% are resistant to metronidazole and 15-20% are resistant to clarithromycin.

With the exception of the Rifabutin-based regimen, **all treatments for Hp should be 14 days duration**.

First Round

CLAMET Quad for 14 days
- PPI standard dose BID
- Clarithromycin 500mg BID
- Amoxicillin 1000mg BID
- Metronidazole 500mg BID

OR

BMT Quad for 14 days
- PPI standard dose BID
- Bismuth subsalicylate 524mg QID
- Metronidazole 375mg QID
- Tetracycline 500mg BID

Second Round

- If CLAMET Quad was used as initial treatment, then use BMT Quad for second round.
- If BMT Quad was used as initial treatment, then use CLAMET Quad or consider Levo-Amox

Third Round

Levo-Amox for 14 days
- PPI standard dose BID
- Levofloxacin 250 mg BID
- Amoxicillin 1000mg BID

Fourth Round

Rif-Amox for 10 days
- PPI standard dose BID
- Rifabutin 150mg BID
- Amoxicillin 1000mg BID

This should only be considered after failure or intolerance of the above three regimens. **Rifabutin has rarely been associated with potentially serious myelotoxicity, that is, low white cell or platelet count.** The pros and cons of giving fourth-line therapy should be decided on a case-by-case basis.

Patient information sheets for each of these regimens are attached below and are available from your PCN website. These one-page information sheets list important additional information about specific Hp treatment regimens including side effects and warnings. Ideally this should be presented and discussed with your patient during an in-clinic visit.

The patient should be reminded of the **importance of completing the entire treatment exactly as prescribed**. For clarity and convenience, particularly with the Quad threapies, it may be helpful to **have the prescription bubble packed** which is a nominal charge at most pharmacies.

If patients have had problems tolerating antibiotics in the past, **administration of probiotics for the entire duration of Hp treatment may improve tolerability and/or improve eradication rates**, although this is a broad generalization and comes at added cost to the patient. If your patient wishes to try this, evidence supports the use of *Lactobacillus* species, *Sacharomyces boulardi*, or multi-species formulations.

PATIENT INFORMATION SHEET

CLAMET based quadruple therapy for *Helicobacter pylori* infection of the stomach

Take the following 4 medications for 14 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Clarithromycin 500mg	1 capsules (500mg)	2x daily
Amoxicillin 500mg	2 capsules (1000mg)	2x daily
Metronidazole 500mg	1 tablet (500mg)	2x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $160** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments.

Clarithromycin (Biaxin®): This antibiotic is frequently used to treat lung and ear infections, but is also effective against *H. pylori*. The most common side effects are taste disturbance (10%), loose stools (5%) and nausea (2%).

Amoxicillin (generic): This drug is commonly used to treat lung and bladder infections, but remains one of the most reliable antibiotics against *H. pylori*. The most common side effects are loose stools (7%) and skin rash (2%). Should a skin rash develop while on this medication, discontinue it immediately and contact your physician. If you have had an adverse reaction to penicillin at any time in the past, you must discuss the nature and severity of the reaction with your doctor to decide about the use of this medication.

Metronidazole (Flagyl®): This antibiotic is used to treat a variety of gastrointestinal infections. The most common side effects are nausea, metallic taste in the mouth and loose stools. It can interact with alcohol to produce flushing, nausea, low blood pressure, heart palpitations or chest discomfort and, therefore, you must not drink any alcohol while taking this drug.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of four drugs without too much difficulty.

Specialist *LINK* | Primary Care Networks Calgary and Area | Calgary Division of Gastroenterology & Hepatology | Alberta Health Services

PATIENT INFORMATION SHEET

BMT based quadruple therapy for *Helicobacter pylori* infection of the stomach

Take the following 4 medications for 14 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Bismuth subsalicylate (Pepto-Bismol®) 262mg	2 caplets (524mg)	4x daily
Metronidazole 250mg	1½ tablets (375mg)	4x daily
Tetracycline 500mg	1 capsule (500mg)	4x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $95** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments.

Bismuth subsalicylate (Pepto-Bismol®): This is an over-the-counter drug commonly used to treat indigestion, which also has antibiotic effects on *H. pylori*. Pepto-Bismol will cause dark coloring of the stool and/or black appearance of the tongue, which disappear after the medication is stopped. Nervous system side effects (i.e. dizziness and confusion) have been reported but are rare. Patients with kidney problems are at higher risk of these side effects and should consult their physician before taking this medication.

Metronidazole (Flagyl®): This antibiotic is used to treat a variety of gut infections. The most common side effects are nausea, metallic taste in the mouth and loose stools. It can interact with alcohol to produce flushing, nausea, low blood pressure, heart palpitations or chest discomfort and, therefore, you must not drink any alcohol while taking this drug.

Tetracycline (generic): This medication is commonly used to treat lung and skin infections, but also has reliable antibiotic effects on *H. pylori*. Side effects occur in less than 5% of patients and include nausea, vomiting, loose stools, and skin rash. Tetracycline sensitizes the skin to the harmful effects of ultraviolet light and, therefore, you must avoid prolonged sun exposure while on this medication.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of four drugs without too much difficulty.

PATIENT INFORMATION SHEET

Levo-Amox based triple therapy for *Helicobacter pylori* infection of the stomach

Take the following 3 medications for 14 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Levofloxacin 250mg	1 tablet (250mg)	2x daily
Amoxicillin 500mg	2 capsules (1000mg)	2x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $110** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments

Levofloxacin (Levaquin®): This antibiotic is most commonly used to treat lung, bladder, sinus, and skin infections, but is also used to treat *H. pylori* after initial failed attempts. It is generally well tolerated. The most common and minor side effects are headache, nausea, and diarrhea. Rare side effects include numbness or tingling in the hands or feet and liver inflammation or jaundice. Additional caution should be used in patients with known liver or kidney problems and in patients with heart rhythm problems. Very rarely, use of this medication has been associated with muscle tendon rupture. Levofloxacin should not be used by patients known to be allergic to antibiotics in the same drug class as ciprofloxacin.

Amoxicillin (generic): This drug is commonly used to treat lung and bladder infections, but remains one of the most reliable antibiotics against *H. pylori*. The most common side effects are loose stools (7%) and skin rash (2%). Should a skin rash develop while on this medication, discontinue it immediately and contact your physician. If you have had an adverse reaction to penicillin at any time in the past, you must discuss the nature and severity of the reaction with your doctor to decide about the use of this medication.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of three drugs without too much difficulty.

PATIENT INFORMATION SHEET

Rif-Amox based triple therapy for *Helicobacter pylori* infection of the stomach

Take the following 3 medications for 10 days. For convenience and clarity of dosing, ask your pharmacist to bubble pack your prescription. This regimen is reserved for patients with *H. pylori* infection that persists despite multiple previous attempts at cure with distinct antibiotic combinations.

Medication and Dosage Form	Dose	Frequency
Proton pump inhibitor (see below for standard doses)	1 pill	2x daily
Rifabutin 150mg	1 tablet (150mg)	2x daily
Amoxicillin 500mg	2 capsules (1000mg)	2x daily
Treatment success will be significantly lower if the medications are not taken exactly as prescribed. **The cost of this regimen is approximately $170** if generic agents are dispensed.		

Proton pump inhibitors: These are very effective and specific blockers of acid production in the stomach. Disrupting the acid environment favoured by *H. pylori* makes it more susceptible to antibiotics. There are six proton pump inhibitors available in Canada, listed by generic and brand names as well as standard dosage form: omeprazole 20mg (Losec®), lansoprazole 30mg (Prevacid®), pantoprazole 40mg (Pantoloc®), rabeprazole 20mg (Pariet®), esomeprazole 40mg (Nexium®), and dexlansoprazole 30mg (Dexilant®). Any of these PPI drugs can be used, as they are equally effective in *H. pylori* treatments.

Rifabutin (Mycobutin®): This antibiotic is usually used to treat tuberculosis, but is also very effective against *H. pylori* due to low prevalence of resistance. Rifabutin is expensive and may take a few days to obtain by your pharmacy. It commonly causes a metallic taste and orange-red discolouration of the urine. About 30% of patients experience headache, nausea, diarrhea, rash, or muscle/joint pain. Rare but potentially serious side effects (<2% incidence) include liver injury or dysfunction, or impairment of bone marrow production of blood cells with risk of fever, infection, or bleeding. In most cases, these rare adverse effects disappear when rifabutin is discontinued, but there a few reports of severe or persistent liver or bone marrow injury.

Amoxicillin (generic): This drug is commonly used to treat lung and bladder infections, but remains one of the most reliable antibiotics against *H. pylori*. The most common side effects are loose stools (7%) and skin rash (2%). Should a skin rash develop while on this medication, discontinue it immediately and contact your physician. If you have had an adverse reaction to penicillin at any time in the past, you must discuss the nature and severity of the reaction with your doctor to decide about the use of this medication.

Additional important information: These and other antibiotics can lead to development of *Clostridium difficile* diarrhea, affect the reliability of the birth control pill, or interact with warfarin (Coumadin®). Talk to your prescribing physician or pharmacist about potential interactions with your specific medications. In women who are pregnant or breastfeeding, *H. pylori* treatment should be deferred. Despite the numerous listed potential adverse effects, most people tolerate this combination of three drugs without too much difficulty.

Patient Name:	Date of Referral:
Date of Birth:	Referring MD:
Calgary RHRN:	Fax:
PHN / ULI:	Today's Date:

CONFIRMATION: **Referral Received**

TRIAGE CATEGORY: **Enhanced Primary Care Pathway**

REFERRAL STATUS: **CLOSED**

DYSPEPSIA

Dear Colleague,

The clinical and diagnostic information you have provided for the above-named patient is consistent with dyspepsia. Based on full review of your referral, it has been determined that **management of this patient within the Enhanced Primary Care Pathway is appropriate, without need for specialist consultation at this time.**

This clinical pathway has been developed by the Calgary Zone Primary Care Network in partnership with the Section of Gastroenterology and Alberta Health Services. These local guidelines are based on best available clinical evidence, and are practical in the primary care setting. This package includes:

1. Focused summary of dyspepsia relevant to primary care
2. Checklist to guide your in-clinic patient review
3. Links to additional resources for this specific condition
4. Clinical flow diagram with expanded detail

This referral is CLOSED.

If you would like to discuss this referral with a Gastroenterologist, call Specialist LINK, a dedicated GI phone consultation service, available 08:00-17:00 weekdays at 403-910-2551 or toll-free 1-855-387-3151.

If your patient completes the Enhanced Primary Care Pathway and remains symptomatic or if your patient's status or symptoms change, a new referral indicating 'completed care pathway' or 'new information' should be faxed to GI Central Access and Triage at 403-944-6540.

Thank you.

Kevin Rioux, MD PhD FRCPC
Medical Lead, GI Central Access and Triage
Section of Gastroenterology

Enhanced Primary Care Pathway: DYSPEPSIA

1. Focused summary of dyspepsia relevant to primary care

Dyspepsia refers to a symptom complex of gastroduodenal origin, characterized by epigastric pain or discomfort that may be triggered by eating and may be accompanied by a sense of abdominal distention or "bloating" and loss of appetite. The Rome III committee on functional GI disorders defines dyspepsia as one or more of the following symptoms:

- Postprandial fullness (postprandial distress syndrome)
- Epigastric pain or burning (epigastric pain syndrome)
- Early satiety

Other symptoms such as belching and nausea may occur. There is frequent overlap between dyspepsia and heartburn, which typifies gastroesophageal reflux (GERD). Irritable bowel syndrome also overlaps with functional dyspepsia, where the predominant symptom complex includes bloating and relief after defecation. Biliary tract pain should also be considered, the classic symptom description being post-prandial (worse with fatty meals) deep-seated right upper quadrant pain that builds over several hours and then dissipates.

Dyspeptic symptoms in the general population are common: estimates as high as 30% of individuals experience dyspeptic symptoms, while few seek medical care. **Although the causes of dyspepsia include esophagitis, peptic ulcer disease, *Helicobacter pylori* infection, celiac disease, and rarely neoplasia, most patients with dyspepsia have no organic disease, with a normal battery of investigations including endoscopy**. The mechanism of this symptom complex is incompletely understood, but likely involves visceral hypersensitivity, alterations in gastric accommodation and emptying and altered central pain processing.

2. Checklist to guide your in-clinic review of this patient with dyspepsia symptoms

☐ Absence of red flag features (weight loss, anemia, iron deficiency, dysphagia, vomiting, age >50y with new symptoms)
☐ Negative urea breath test (must be done off PPI, H_2-receptor antagonists, antacids for minimum of 3 days, and off all antibiotics for minimum of 4 weeks)
☐ Lifestyle modifications have been discussed and patient has incorporated these into their initial treatment plan (smaller meals, avoidance of identified food triggers, appropriate weight loss, elevation of head of bed, smoking cessation)
☐ Patient adherent to trial of PPI (can start once daily then escalate to twice daily, 30 minutes before breakfast and supper for minimum of 8 weeks)

Enhanced Primary Care Pathway: DYSPEPSIA

3. Links to additional resources for physicians and patients

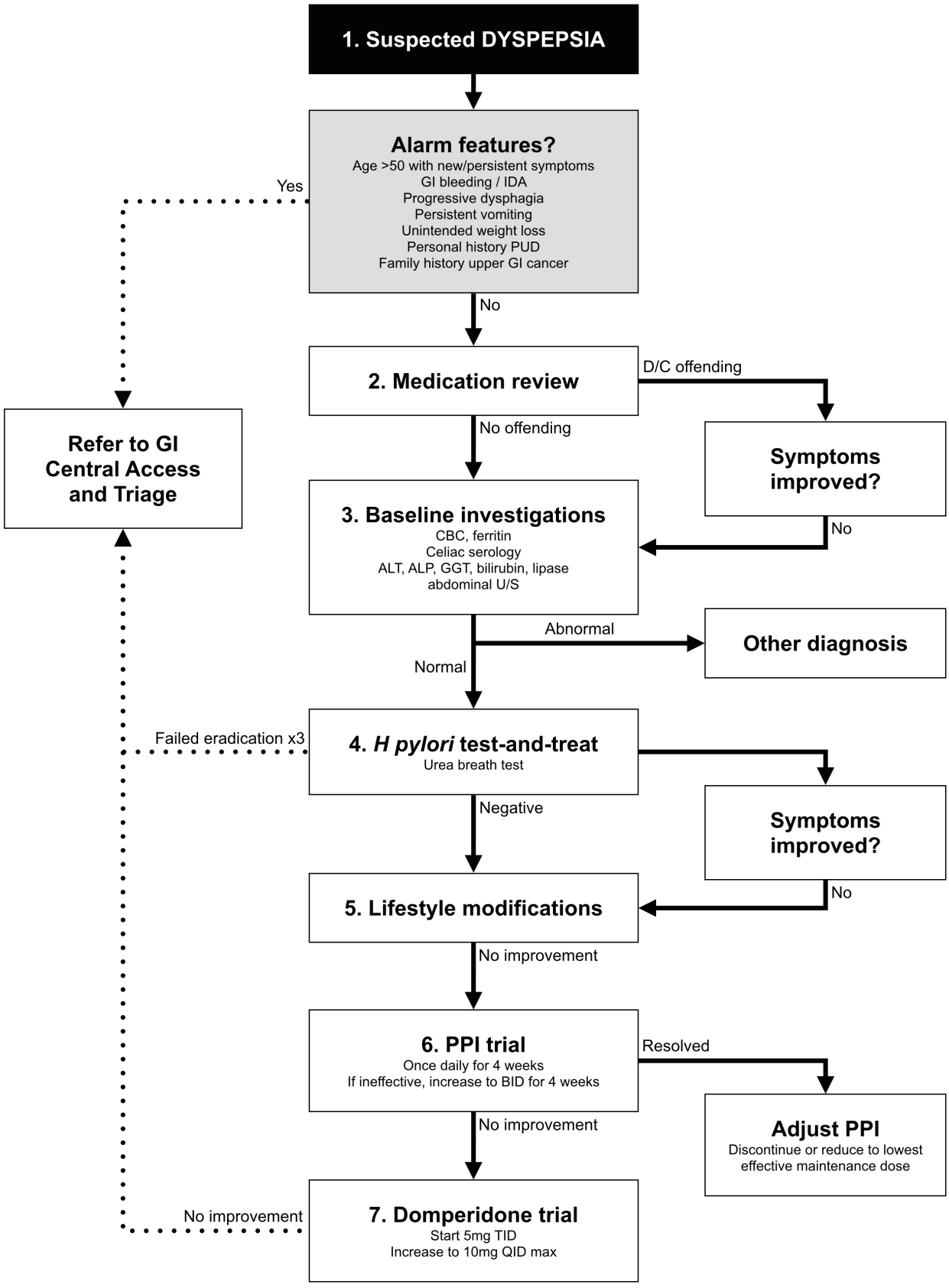
Calgary GI Division http://www.calgarygi.com
MyHealth.Alberta.ca https://myhealth.alberta.ca/health/pages/conditions.aspx?Hwid=tm6322
Canadian Digestive Health Foundation http://www.cdhf.ca/en/disorders/details/id/20
UpToDate® – *Beyond the Basics* Patient Information (freely accessible) http://www.uptodate.com/contents/upset-stomach-functional-dyspepsia-in-adults-beyond-the-basics?source=search_result&search=dyspepsia+patient+info&selectedTitle=2~150

4. Clinical flow diagram with expanded detail

This AHS Calgary Zone pathway incorporates the most current evidence-based clinical guidelines for diagnosis and management of dyspepsia, from both Gastroenterology and Primary Care literature:

Miwa *et al.* Evidence-based clinical practice guidelines for functional dyspepsia. J Gastroenterol. 50:125-39, 2015
Ansari *et al.* Initial management of dyspepsia in primary care: an evidence-based approach. Br J Gen Pract. 63:498-9, 2013
Diagnosis and treatment of chronic undiagnosed dyspepsia in adults. Toward Optimized Practice http://www.topalbertadoctors.org/cpgs/3294128
American Society of Gastrointestinal Endoscopy Standards of Practice Committee. The role of endoscopy in dyspepsia. Gastrointest Endosc 66:1071-5, 2007

The following is a best-practice clinical pathway for management of dyspepsia in the primary care medical home, which includes a flow diagram and expanded explanation of treatment options:


1. Suspected DYSPEPSIA
Alarm features?
Age >50 with new/persistent symptoms
GI bleeding / IDA
Progressive dysphagia
Persistent vomiting
Unintended weight loss
Personal history PUD
Family history upper GI cancer
Yes
No
Refer to GI Central Access and Triage
2. Medication review
D/C offending
No offending
Symptoms improved?
No
3. Baseline investigations
CBC, ferritin
Celiac serology
ALT, ALP, GGT, bilirubin, lipase
abdominal U/S
Abnormal
Other diagnosis
Normal
Failed eradication x3
4. H pylori test-and-treat
Urea breath test
Negative
Symptoms improved?
No
5. Lifestyle modifications
No improvement
6. PPI trial
Once daily for 4 weeks
If ineffective, increase to BID for 4 weeks
Resolved
Adjust PPI
Discontinue or reduce to lowest effective maintenance dose
No improvement
No improvement
7. Domperidone trial
Start 5mg TID
Increase to 10mg QID max

Flow Diagram: DYSPEPSIA Diagnosis and Management - Expanded Detail

1. **Establish the diagnosis of dyspepsia** as defined above through history and physical examination, excluding worrisome features or red flags. In the presence of any red flags, referral to Gastroenterology for consideration of urgent endoscopic investigation is recommended, even though the predictive value of these features is somewhat limited.

2. **Review of the patient's medication profile** should be undertaken to try to identify obvious culprits such as ASA/NSAIDs/COX-2 inhibitors, steroids, bisphosphonates, calcium channel blockers, antibiotics, iron or magnesium supplements. Any new or recently prescribed medication, over the counter or herbal/natural product may be implicated as virtually all medications can cause GI upset in some patients.

3. **Baseline Investigations** aimed at identifying concerning features or clear etiologies:

    - CBC and ferritin
    - Anti-tissue transglutaminase has >95% sensitivity to rule out celiac disease
    - ALT, ALP, GGT, and lipase, aimed at identifying a hepatobiliary or pancreatic source of pain
    - If pain is consistent with biliary colic or liver enzymes or lipase are abnormal or there is a palpable abdominal mass, obtain a trans-abdominal ultrasound.
    - Upper GI series may be considered, but is low yield for relevant findings, as is endoscopy

4. **Test and treat *Helicobacter pylori*** by urea breath test (UBT). This strategy is based on evidence that some dyspeptic patients are colonized by *H. pylori* and will have underlying peptic ulcer disease or gastritis.
    - If the UBT is positive, recommend standard triple eradication therapy: amoxicillin 1g BID + clarithromycin 500mg BID + any standard dose PPI BID (see below) for 10-14 days; it is less expensive to provide each component medication for 10-14d than branded triple therapy packs for 14d. Confirm eradication by repeat UBT 4 weeks after completion of antibiotics.
        - If the patient is penicillin-allergic, metronidazole 500mg BID can be substituted
        - If the patient is clarithromycin-allergic, use second line therapy below
    - If the patient fails first-line therapy above, second line quadruple eradication therapy is recommended for 10 days: any PPI BID plus bismuth subsalicylate 525mg QID (=Pepto-Bismol 2 caplets or 2 tablespoons QID), metronidazole 250mg QID and tetracycline 500mg QID. **Bubble pack for patient ease and adherence.**
    - If the patient fails second line therapy (or is tetracycline-allergic), use levofloxacin-based regimen: any standard dose PPI BID + amoxicillin 1g BID + levofloxacin 250mg BID, all for 10 days
    - Standard doses of PPIs are: omeprazole 20mg, rabeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg, esomeprazole 40mg, dexlansoprazole 30mg)
    - **ALWAYS discuss with your patient the possible minor or serious adverse effects of antibiotics**
    - If fails third line therapy, then refer to Gastroenterology.

5. **Lifestyle modification.** There are few studies to support specific dietary recommendations, but a trial of various dietary exclusions under the guidance of a nutritionist or registered dietician may be helpful, including avoidance of lactose and foods high in fructose (FODMAPs).

6. **Empiric anti-secretory medication trial.** In the absence *H. pylori* infection or continued symptoms despite successful *H. pylori* eradication, a trial of standard dose PPI for 4-8 weeks may benefit some patients. PPIs are favoured over H2-receptor antagonists. Initial therapy should be once daily, 30min before breakfast. If there is no significant symptomatic improvement after 4 weeks, step up to BID dosing or switch to another PPI. If symptoms are then controlled, it is advisable to titrate down to the lowest effective dose.

7. **Trial of motility agents.** Although delayed gastric emptying can be demonstrated in 30-80% of patients with dyspepsia, gastric emptying studies are not part of routine investigation of dyspepsia. Prokinetic agents improve gastric emptying, and some patients may find clinical benefit. Domperidone can be used in escalating doses, suggest starting at 5mg TID-AC, up to 10mg PO QID as a 2-4 week trial.

    There are insufficient data to recommend the routine use of bismuth, antacids, simethicone, misoprostol, anti-cholinergics, anti-spasmodics, TCAs, SSRIs, herbal therapies, probiotics or psychological therapies in functional dyspepsia. However, these therapies may be of benefit in some patients, and thus a trial with assessment of response may be reasonable and is unlikely to cause harm.

Patient Name:	Date of Referral:
Date of Birth:	Referring MD:
Calgary RHRN:	Fax:
PHN / ULI:	Today's Date:

CONFIRMATION: **Referral Received**

TRIAGE CATEGORY: **Enhanced Primary Care Pathway**

REFERRAL STATUS: **CLOSED**

GERD

Dear Colleague,

The clinical and diagnostic information you have provided for the above-named patient is consistent with gastroesophageal reflux disease. Based on full review of your referral, it has been determined that **management of this patient within the Enhanced Primary Care Pathway is appropriate, without need for specialist consultation at this time.**

This clinical pathway has been developed by the Calgary Zone Primary Care Network in partnership with the Section of Gastroenterology and Alberta Health Services. These local guidelines are based on best available clinical evidence, and are practical in the primary care setting. This package includes:

1. Focused summary of GERD relevant to primary care
2. Checklist to guide your in-clinic patient review
3. Links to additional resources for this specific condition
4. Clinical flow diagram with expanded detail

This referral is CLOSED.

If you would like to discuss this referral with a Gastroenterologist, call Specialist LINK, a dedicated GI phone consultation service, available 08:00-17:00 weekdays at 403-910-2551 or toll-free 1-855-387-3151.

If your patient completes the Enhanced Primary Care Pathway and remains symptomatic or if your patient's status or symptoms change, a new referral indicating 'completed care pathway' or 'new information' should be faxed to 403-944-6540.

Thank you.

Kevin Rioux, MD PhD FRCPC
Medical Lead, Central Access and Triage
Section of Gastroenterology

Enhanced Primary Care Pathway: GERD

1. Focused summary of GERD relevant to primary care

The reflux of gastric contents into the esophagus is a normal physiological phenomenon. Reflux is deemed pathological when it causes esophageal injury or produces symptoms that are troublesome to the patient, typically heartburn and regurgitation, a condition known as gastroesophageal reflux disease. GERD is very common in primary care practice and easy to recognize in its typical form, generally requiring no initial investigations. Treatment at the primary care level is focused on lifestyle and dietary modifications to avoid GERD triggers and achieve healthy body weight, and optimal use of proton pump inhibitor.

If heartburn is a dominant symptom, the differential diagnosis includes various causes of esophagitis (infectious, pill-induced, eosinophilic), peptic ulcer disease, non-ulcer dyspepsia, coronary artery disease, biliary and pancreatic disease.

In some patients, GERD has a wider spectrum of symptoms including chest pain, dysphagia, globus sensation, odynophagia, nausea and waterbrash. As reflux tends to occur after eating, there is often overlap of GERD and dyspepsia, which refers to postprandial epigastric discomfort.

A presumptive diagnosis of GERD can be made in patients with any of the clinical symptoms described above, and generally no investigations are required as part of initial workup. Screening for *H. pylori* is not recommended in GERD. Most patients with GERD will have improvement or resolution of symptoms when treated with PPI.

Endoscopy is warranted in patients presenting with dysphagia or other alarm features, and in those refractory to adequate initial and optimized PPI treatments. Esophageal pH or impedence-pH reflux monitoring studies are sometimes arranged by GI after endoscopy.

GERD can be complicated by Barrett's esophagus, esophageal stricture and, rarely, esophageal cancer. Screening for Barrett's esophagus is another indication for endoscopy, but specific criteria must be met:

- ☐ **Chronic GERD (≥10 years) <u>plus two or more risk factors</u>:**
  - ☐ >50 years of age
  - ☐ Male gender
  - ☐ Caucasian
  - ☐ BMI ≥30
  - ☐ Waist circumference >35" for females or >40" for males
  - ☐ Hiatal hernia (demonstrated radiographically)
  - ☐ Family history of esophageal cancer or Barrett's
- ☐ **GERD is well controlled with once or twice daily PPI**

2. Checklist to guide your in-clinic review of this patient with GERD symptoms

- ☐ Symptoms of GERD without alarm features
- ☐ If dyspepsia overlaps with GERD, follow Enhanced Primary Care Pathway: DYSPEPSIA, available at www.calgarygi.com
- ☐ Lifestyle factors that contribute to GERD have been identified and discussed with your patient. If applicable, weight loss is essential to management of GERD, and your patient should be guided and monitored to achieve specific goals.
- ☐ Patient adherent to initial trial of PPI for 8 weeks, followed by review and optimization

3. Links to additional resources for physicians and patients

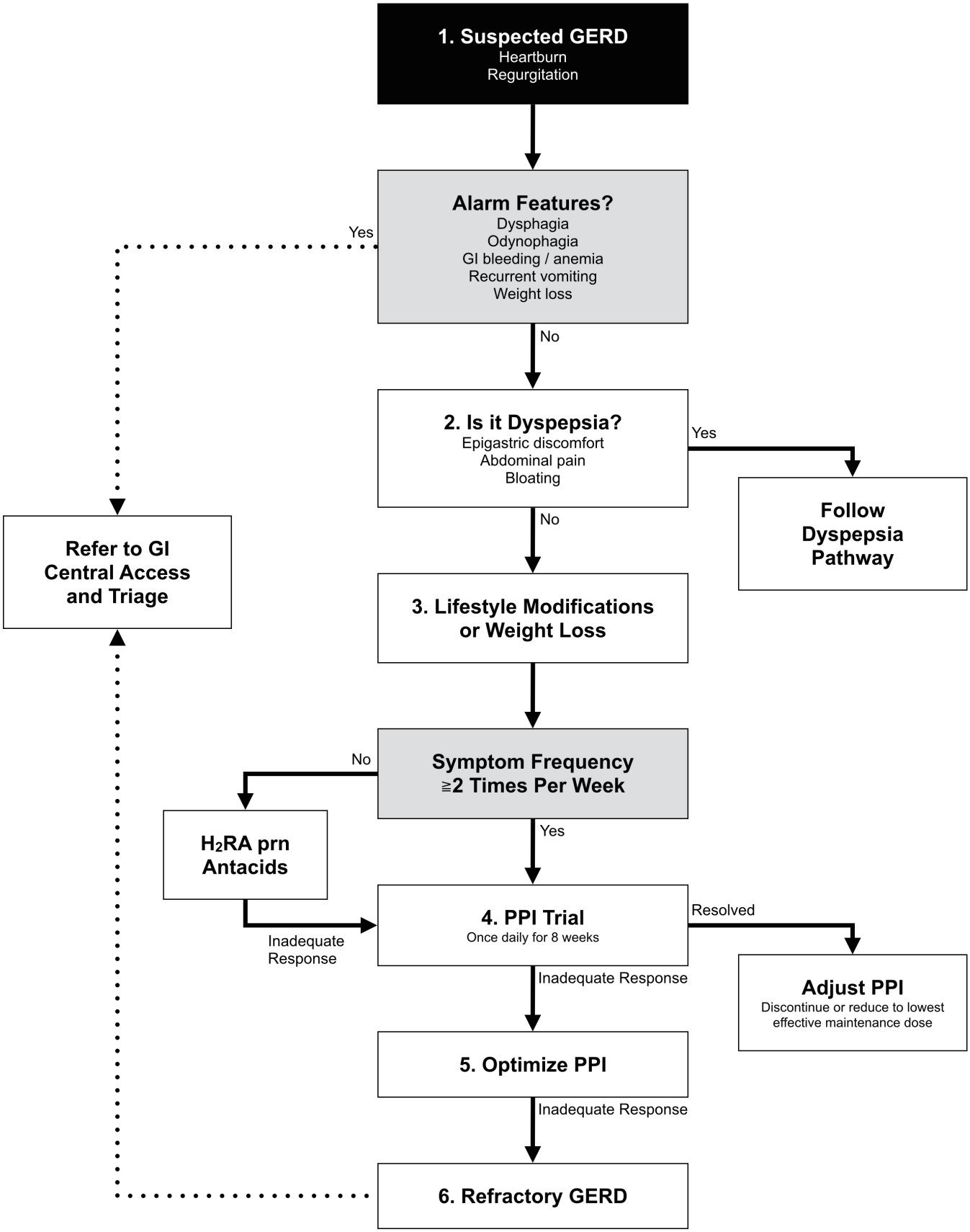
Calgary GI Division http://www.calgarygi.com
Weight Management MyHealth.Alberta.ca https://myhealth.alberta.ca/health/pages/conditions.aspx?Hwid=aa122915
Weight Wise Adult Community Program http://www.albertahealthservices.ca/services.asp?pid=service&rid=1060802
Alberta Healthy Living Program http://www.albertahealthservices.ca/services.asp?pid=service&rid=1005671
Canadian Digestive Health Foundation http://www.cdhf.ca/en/disorders/details/id/11
UpToDate® – *Beyond the Basics* Patient Information (freely accessible) http://www.uptodate.com/contents/acid-reflux-gastroesophageal-reflux-disease-in-adults-beyond-the-basics?source=search_result&search=GERD+beyond+the+basics&selectedTitle=2~150

4. Clinical flow diagram with expanded detail

This AHS Calgary Zone pathway incorporates the most current evidence-based clinical guidelines for diagnosis and management of GERD from both Gastroenterology and Primary Care literature:

Katz *et al.* Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 108:308-28, 2013
Flook *et al.* Approach to gastroesophageal reflux disease in primary care: Putting the Montreal definition into practice. Can Fam Physician. 54:701-5, 2008
Kahrilas *et al.* American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 135:1392-1413, 2008.
Armstrong *et al*. Canadian consensus conference on the management of gastroesophageal reflux disease in adults. Can J Gastroenterol. 19:15-35, 2005
Treatment of Gastroesophageal Reflux Disease in Adults. Toward Optimized Practice http://www.topalbertadoctors.org/cpgs/3294128

The following is a best-practice clinical pathway for management of GERD in the primary care medical home, which includes a flow diagram and expanded explanation of treatment options:


1. Suspected GERD
Heartburn
Regurgitation
Alarm Features?
Dysphagia
Odynophagia
GI bleeding / anemia
Recurrent vomiting
Weight loss
Yes
No
Refer to GI Central Access and Triage
2. Is it Dyspepsia?
Epigastric discomfort
Abdominal pain
Bloating
Yes
Follow Dyspepsia Pathway
No
3. Lifestyle Modifications or Weight Loss
Symptom Frequency ≥2 Times Per Week
No
Yes
H2RA prn Antacids
Inadequate Response
4. PPI Trial
Once daily for 8 weeks
Resolved
Adjust PPI
Discontinue or reduce to lowest effective maintenance dose
Inadequate Response
5. Optimize PPI
Inadequate Response
6. Refractory GERD

Flow Diagram: GERD Diagnosis and Management - Expanded Detail

1. **A presumptive diagnosis of GERD can be made in patients with typical symptoms of heartburn and regurgitation.** The presence of these symptoms is quite specific for GERD. If patients with suspected GERD have chest pain as a dominant feature, cardiac causes should first be excluded. In the presence of any red flags, referral to Gastroenterology for consideration of urgent endoscopic investigation is recommended, even though the predictive value of some of these features is somewhat limited.

2. **Features of dyspepsia should be sought.** If the patient's dominant symptom is postprandial epigastric pain and bloating, please refer to the Enhanced Primary Care DYSPEPSIA pathway (available at www.calgarygi.com). GERD and dyspepsia clinical pathways are sufficiently distinct and, in particular, the initial assessment of dyspepsia involves testing for *H. pylori* and other laboratory investigations, which are not required in patients with GERD.

3. **Non-pharmacological principles of GERD management.**

    - Weight loss in patients who are overweight, or in those who have recently gained weight even if normal body mass index
    - Head of bed elevation (blocks or foam wedges) and avoid meals 3h before bedtime if nocturnal GERD
    - Elimination of prototypic GERD triggers (smoking, alcohol, caffeine, carbonated beverages, spicy/fatty/acidic foods, chocolate and mint) is reasonable, but is not supported by clear evidence of physiological or clinical improvement of GERD. Rather than food triggers, it is likely higher yield to provide dietary counseling to GERD patients to affect weight loss.

4. **Trial of proton pump inhibitor**

    - Although PPIs are the mainstay of GERD therapy, there remains a role for H_2RA or antacids (alginates, Ca/Mg/Al salts) in patients with mild, infrequent, episodic symptoms. These provide rapid on-demand relief of heartburn and avoid prematurely committing some patients to long-term use of PPI.
    - For patients with more troublesome symptoms, PPI provides more effective long-term relief.
    - An 8-week trial of standard once-daily PPI is recommended (omeprazole 20mg, rabeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg, esomeprazole 40mg, dexlansoprazole 30mg). There are no major differences in efficacy between these agents. All PPI should be administered 30-60 minutes before breakfast with the exception of dexlansoprazole, which is a dual delayed release formulation that can be taken at any time of day regardless of food intake.
    - If symptoms are resolved, PPI should be titrated to lowest effective maintenance dose (there are half-standard doses of most PPI available e.g. lansoprazole 15mg) or even attempt to discontinue, especially if weight reduction has been achieved.
    - Potential side effects of PPI include headache and diarrhea, which may not occur when switched to a different PPI. There is some evidence that PPI use is associated with *C. difficile* colitis and other enteric infections, and should be used with caution in certain patients at risk.

5. **Optimize PPI**

    - It is estimated that one-third of patients with typical GERD will not adequately respond to PPI. Factors that predict PPI failure are obesity and poor adherence to PPI treatment.
    - Patient non-adherence to treatment with PPI is common. Confirm that the patient has taken the intended dose of PPI on a daily basis, 30 minutes before breakfast for 8 weeks.
    - If suboptimal response, switch to another once daily PPI (e.g. esomeprazole) or try high-dose PPI (standard dose PPI twice daily 30 minutes before breakfast and supper or dexlansoprazole 60mg once daily) for an additional 8 weeks. The clinical and pharmacodynamic data to support this is actually fairly limited, however.

6. **Refractory GERD.** Patients with persistent troublesome GERD symptoms should be referred to GI Central Access and Triage for diagnostic evaluation (endoscopy ± pH/impedance reflux monitoring) to discern GERD from non-GERD etiologies.

Patient Name:	Date of Referral:
Date of Birth:	Referring MD:
Calgary RHRN:	Fax:
PHN / ULI:	Today's Date:

CONFIRMATION: **Referral Received**

TRIAGE CATEGORY: **Enhanced Primary Care Pathway**

REFERRAL STATUS: **CLOSED**

IBS

Dear Colleague,

The clinical and diagnostic information you have provided for the above-named patient is consistent with irritable bowel syndrome (IBS). Based on full review of your referral, it has been determined that **management of this patient within the Enhanced Primary Care Pathway is appropriate, without need for specialist consultation at this time.**

This clinical pathway has been developed by the Calgary Zone Primary Care Network in partnership with the Section of Gastroenterology and Alberta Health Services. These local guidelines are based on best available clinical evidence, and are practical in the primary care setting. This package includes:

1. Focused summary of IBS relevant to primary care
2. Checklist to guide your in-clinic patient review
3. Links to additional resources for this specific condition
4. Clinical flow diagram with expanded detail

This referral is CLOSED.

If you would like to discuss this referral with a Gastroenterologist, call Specialist LINK, a dedicated GI phone consultation service, available 08:00-17:00 weekdays at 403-910-2551 or toll-free 1-855-387-3151.

If your patient completes the Enhanced Primary Care Pathway and remains symptomatic or if your patient's status or symptoms change, a new referral indicating 'completed care pathway' or 'new information' should be faxed to GI Central Access and Triage at 403-944-6540.

Thank you.

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Section of Gastroenterology

Enhanced Primary Care Pathway: IBS

1. Focused summary of IBS relevant to primary care

Irritable bowel syndrome is a common symptom complex characterized by **chronic abdominal pain and abnormal bowel function** in absence of organic cause. These key features of IBS can be widely variable in severity and may remit and recur, often being affected by dietary factors and various stressors. **Relief of abdominal discomfort after bowel movement** is a defining feature**.** Bowel dysfunction includes frequent bowel movements, fecal urgency and even incontinence, altered stool form (hard/lumpy or loose/watery), incomplete evacuation, straining at stool, and passage of copious mucus.

IBS is frequently associated with other gastrointestinal symptoms including bloating, flatulence, nausea, burping, early satiety, gastroesophageal reflux, and dyspepsia. Extra-intestinal symptoms also frequently occur in IBS patients including dysuria and frequent, urgent urination, widespread musculoskeletal pain, dysmenorrhea, dyspareunia, fatigue, anxiety, and depression.

Diagnostic criteria (e.g. Rome or Manning Criteria) for IBS were developed for uniformity of patient recruitment in clinical trials. In clinical practice, such criteria only provide a framework for assessing patients with suspected IBS; indeed these criteria alone are far better for ruling out IBS than ruling it in.

The confident diagnosis of IBS relies on presence of foundational symptoms (*i.e.* Rome III criteria), recognition of intestinal and extra-intestinal symptoms and psychological stressors that support the IBS diagnosis, detailed medical history and physical examination as well as judicious use of investigations to identify red flag features and exclude organic conditions that mimic IBS.

Treatment of IBS involves initial reassurance, dietary, psychological, behavioral interventions, pharmacotherapy based on dominant symptoms, and scheduled patient clinical review, reappraisal, support, and guidance.

2. Checklist to guide your in-clinic review of this patient with IBS symptoms

- ☐ Rome III criteria for IBS: Recurrent **abdominal pain** ≥3 days per month in the last three months, and onset of pain associated with **change of frequency or form of stool**, and **pain relieved by defecation**
- ☐ Absence of red flag features (bleeding, anemia, weight loss, nocturnal or progressive symptoms, onset after age 50)
- ☐ No family history of inflammatory bowel disease, colorectal cancer, or celiac disease

Enhanced Primary Care Pathway: IBS

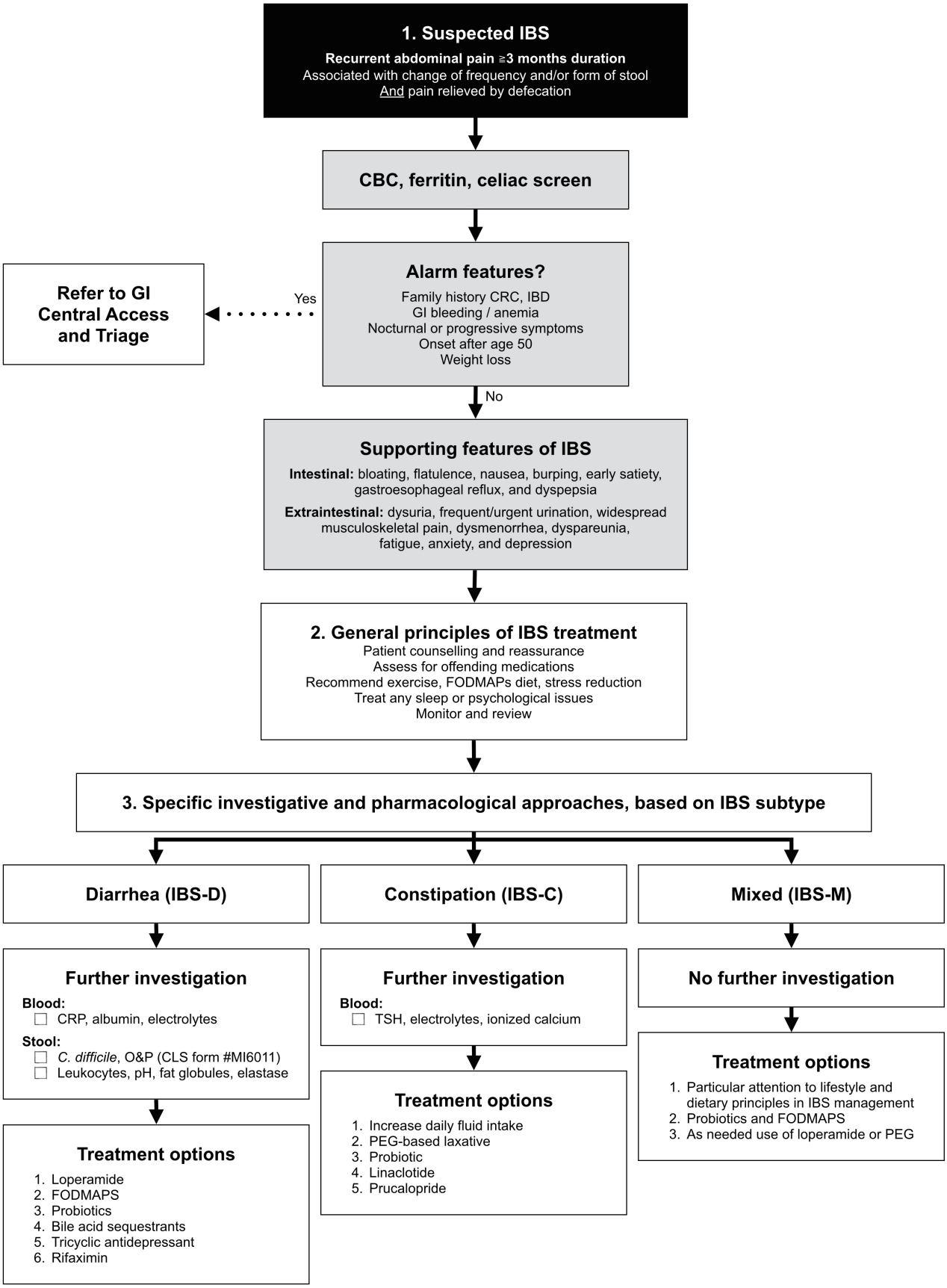
3. Links to additional resources for physicians and patients
Calgary GI Division http://www.calgarygi.com
MyHealth.Alberta.ca https://myhealth.alberta.ca/health/pages/conditions.aspx?Hwid=hw117851
Canadian Digestive Health Foundation http://www.cdhf.ca/en/disorders/details/id/12
UpToDate® – *Beyond the Basics* Patient Information (freely accessible) http://www.uptodate.com/contents/irritable-bowel-syndrome-beyond-the-basics?source=see_link

4. Clinical flow diagram with expanded detail

This AHS Calgary Zone pathway incorporates the most current evidence-based clinical guidelines for diagnosis and management of IBS, from both Gastroenterology and Primary Care literature:

Weinberg *et al.* American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology 147:1146-8, 2015.
Wilkins *et al.* Diagnosis and management of IBS in adults. American Family Physician 86:419-426, 2012
Spiller *et al.* Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 56:1770-98, 2007

The following is a best-practice clinical care pathway for management of irritable bowel syndrome in the primary care medical home, which includes a flow diagram and expanded explanation of treatment options:


1. Suspected IBS
Recurrent abdominal pain ≥3 months duration
Associated with change of frequency and/or form of stool
And pain relieved by defecation
CBC, ferritin, celiac screen
Alarm features?
Family history CRC, IBD
GI bleeding / anemia
Nocturnal or progressive symptoms
Onset after age 50
Weight loss
Yes
Refer to GI Central Access and Triage
No
Supporting features of IBS
Intestinal: bloating, flatulence, nausea, burping, early satiety, gastroesophageal reflux, and dyspepsia
Extraintestinal: dysuria, frequent/urgent urination, widespread musculoskeletal pain, dysmenorrhea, dyspareunia, fatigue, anxiety, and depression
2. General principles of IBS treatment
Patient counselling and reassurance
Assess for offending medications
Recommend exercise, FODMAPs diet, stress reduction
Treat any sleep or psychological issues
Monitor and review
3. Specific investigative and pharmacological approaches, based on IBS subtype
Diarrhea (IBS-D)
Further investigation
Blood:
CRP, albumin, electrolytes
Stool:
C. difficile, O&P (CLS form #MI6011)
Leukocytes, pH, fat globules, elastase
Treatment options
1. Loperamide
2. FODMAPS
3. Probiotics
4. Bile acid sequestrants
5. Tricyclic antidepressant
6. Rifaximin
Constipation (IBS-C)
Further investigation
Blood:
TSH, electrolytes, ionized calcium
Treatment options
1. Increase daily fluid intake
2. PEG-based laxative
3. Probiotic
4. Linaclotide
5. Prucalopride
Mixed (IBS-M)
No further investigation
Treatment options
1. Particular attention to lifestyle and dietary principles in IBS management
2. Probiotics and FODMAPS
3. As needed use of loperamide or PEG

Flow Diagram: IBS Diagnosis and Management - Expanded Detail

1. **Diagnosis of IBS** is based on Rome III criteria of altered bowel habit and abdominal pain relieved by bowel movement. IBS requires very little initial laboratory investigation – CBC, ferritin, and celiac disease screen according to most guidelines. The fecal immunochemical test (FIT) has not been validated for investigation of IBS-like symptoms; ordering FIT in this circumstance is inappropriate. Anemia or other red flag features increase the likelihood of organic disease and mandate referral to GI. Absence of red flags, however, does not completely exclude the possibility of organic disease. Various other intestinal and extraintestinal features often co-exist with IBS and provide support to the diagnosis. It is estimated that unrecognized organic disorders will be present in about 15% of patients who meet Rome III criteria and do not have alarm features. The most common diseases that are mislabeled as IBS are celiac disease, Crohn's disease, and microscopic colitis. If C-reactive protein is ≤ 5 mg/L, the probability of IBD is ≤1%. GI cancers are very unlikely in patients that meet usual criteria for IBS.

   A detailed medical history and physical examination should be performed at presentation to assess for a multitude of other conditions that mimic IBS. A careful review of medications should be performed to identify ones that may be causing GI side effects (e.g. PPI, ASA/NSAIDs, laxatives/antacids, iron/calcium/magnesium supplements, calcium channel blockers, antidepressants, opioids, diuretics, herbal products).

2. **General principles of IBS treatment.** All patients with IBS will benefit from lifestyle and dietary modifications, and this may be all that is required in those with mild or intermittent symptoms that do not affect quality of life. Key to long-term effective management of IBS is to provide patient reassurance of the initial diagnosis IBS and offer points of reassessment and reappraisal to establish a therapeutic relationship. Connecting patients with resources for diet, exercise, stress reduction, and psychological counseling is important. Screen for and treat any underlying sleep or mood disorder.

3. **Specific approaches based on IBS subtype.** There are three clinical phenotypes of IBS: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and mixed pattern alternating diarrhea and constipation (IBS-M). Categorizing IBS by dominant GI symptom guides focused use of a few additional investigations (particularly in IBS-D), but also guides specific treatment approaches. Use of pharmaceuticals in IBS is generally reserved for those who have not adequately responded to dietary and lifestyle interventions, or in those with moderate or severe symptoms that impair quality of life.

   Pain and bloating is a defining feature of IBS and, in some patients, these features are severe or frequent enough to affect quality of life. Antispasmodics may be beneficial in managing or aborting acute episodes of pain, and patients often take reassurance in having these on-demand treatments available. For chronic IBS pain, tricyclic antidepressants have shown benefit, and may have added benefits in those patients with mood or sleep issues.

   <u>In absence of alarm features</u>, what would prompt referral for GI consultation and possible colonoscopy? Colonoscopy may be helpful in patients with diarrhea predominance who have persistent symptoms or limited benefit from usual treatments. This is mainly to assess for Crohn's disease and microscopic colitis. In patients with constipation predominance or alternating diarrhea and constipation, colonoscopy is very unlikely to yield relevant findings.

Principles and Specifics of IBS Management by Subtype

All subtypes of IBS	
Exercise	Moderate to vigorous exercise for 20-60 minutes 3-5x per week
Soluble Fibre	Use in IBS remains controversial, as may be beneficial in some but detrimental in others. Reasonable to try psyllium husk one-half to one tablespoon daily. Insoluble fibre like bran is not beneficial.
Probiotics	Bifidobacterium infantis (Align®) 1 capsule/d ($40/mo.) *Lactobacillus plantarum* 229v (TuZen®)1-2 capsules/d ($40-80/mo.)
Antispasmodics	Peppermint oil (0.2 to 0.275mL caps, enteric coated) 2 capsules BID ($20-25/mo.) Hyoscine Butylbromide (Buscopan®) 10mg TID-QID ($25-40/mo.) Dicyclomine hydrochloride (Bentylol®) 20mg TID-QID ($25-40/mo.) Pinaverium Bromide (Dicetel®) 50-100mg TID ($50-75/mo.) Trimebutine (Modulon®) 100-200mg TID ($40-80/mo.) All prescribed antispasmodic medications should be fully discussed with the patient in terms of specific risks and side effects and appropriateness of use in context of their full medical history
Antidepressants	Nortriptyline or amitriptyline 10-25 mg qhs, dose escalate by 10-25 mg/wk May require 25-150mg/d ($20-60/mo.); usually takes 2-3 mos. for peak effect Particularly useful in patients with diarrhea and pain predominance or sleep issues/anxiety/depression Use with caution in patients at risk of prolonged QT; note somnolence and anticholinergic side effects Latest IBS technical review does not endorse use of SSRIs
Complementary Therapies	Psychological treatments Mindfulness-based stress reduction (www.thebreathproject.org) Hypnotherapy Accupuncture Yoga (www.yogacalgary.ca)
Diarrhea-Predominant IBS	
Antidiarrheals	Loperamide (Imodium®) 2-4mg BID ($25-50/mo. OTC) Cholestyramine powder (Questran®, Olestyr®) or colestipol (Colestid®) tablets 1-4g po OD-TID Especially useful post-cholecystectomy. Advise regarding timing with other medications to avoid interaction; if long term use, risk of fat soluble vitamin deficiencies
FODMAPs	Canadian Digestive Health Foundation cdhf.ca/bank/document_en/32-fodmaps.pdf
Gluten Avoidance	Nonceliac gluten sensitivity
Antibiotics	Rifaximin (Zaxine®) 550mg 3x/daily for 2 weeks which costs ~$325!
Constipation-Predominant IBS	
PEG-based Laxatives	Mira-Lax® or Lax-a-Day® 17-34g/d ($25-50/mo.)
Prokinetics	Linaclotide (Constella®) 145-290µg/d 30 minutes before breakfast ($100-160/mo.) Procalopride (Resotran®) 2mg/d, 4 week trial ($120/mo.)