ACID REFLUX

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Acid reflux is a normal event, for short periods throughout the day, but from a medical point of view, we are dealing with patients who complain of acid reflux symptoms, and have abnormal amounts of acid reflux. On accurate testing (which is considered slightly invasive, requiring a small tube to be inserted through the nose into the esophagus and left there for a 24-hour period), patients with reflux disease usually have more than a normal amount of acid present in the esophagus. Normal is defined by testing normal healthy volunteers who do not have reflux disease. The normal amount is 4% (which is just under 60 minutes per 24 hours, and is mostly just after meals).

The classic symptoms of heartburn and regurgitation are considered to be highly accurate for abnormal reflux, which is also called GERD. GERD (gastroesophageal reflux disease) is medically defined as reflux symptoms causing the patient to consult with a physician, or associated with signs of disease, even if asymptomatic, which are recognized as being related to acid reflux.

Contrary to a number of opinions expressed on various Internet sites and by "alternative" practitioners, there is absolutely no doubt that GERD is related to abnormal amounts of acid getting into the esophagus, from the stomach. This has been established by many studies of healthy volunteers and patients, over many years, and is the reason that reflux symptoms can be treated using over-the-counter antacids (such as Tums, Rolaids, or Gaviscon), H2 blockers such as Zantac (ranitidine) and Pepcid (famotidine) and PPI's (proton pump inhibitors such as omeprazole, pantoprazole and several other similar agents).

I have reviewed a number of these websites and opinions by "alternative" practitioners, and I am surprised at the theories being proposed. Firstly they ignore very well-established and scientific research. Secondly they sometimes suggest that doctors, and especially gastroenterologists, are working with pharmaceutical companies in suppressing truth, and curative treatment. These people are confusing the issue, and feeding into a “conspiracy theory”. They are also, indirectly or directly, disturbing to those of us who are trying to help patients in a conventional & scientific manner. Suggestions that reflux symptoms should be treated with acid, such as hydrochloric acid, or betaine HCl, or even vinegar and lemon juice, are completely bizarre, and potentially dangerous, in my opinion. I have had several patients say that they felt terrible after trying this treatment, and I have one patient who appears to have developed a precancerous change after trying this treatment.

For the above reasons, we can only discuss and treat your GERD if we agree that the problem is abnormal amounts of acid irritating or damaging the esophageal lining. We know that the total amount of acid produced by the stomach in GERD patients may be normal or even low, but the problem is that the acid is getting through the lower esophageal sphincter, whether it is persistently weak, or has periods of weakness (TLESR’s – ie transient lower esophageal sphincter relaxations). We do not have good medication to correct the sphincter defect, so we are left with treatment which works very effectively, by reducing gastric acid production.

Currently there are some drugs which can improve sphincter pressure or sphincter function (eg domperidone), but often these are not well-tolerated, not very effective, and/or have potential serious side effects. We use some of these in specific circumstances, for short periods.

While there is an assumption that we are primarily prescribing drugs, we are very interested in lifestyle issues which will be outlined below. The reasons some physicians tend not to spend as much time on these issues as the patient would like, is usually because these measures are only weakly effective, for the severity of acid reflux that we (as specialists) are seeing in patients, especially those who are referred to us (which is a small fraction of all patients with GERD) or have evidence at endoscopy that the esophageal lining is damaged (acutely inflamed). This latter group is defined as having "erosive esophagitis", and this is a subset of all GERD patients, probably the 10-20% who have the worst amounts of acid reflux. This group seems to include those at risk for esophageal cancer, and also those patients who seem to need, and respond well to, PPI therapy. This group is also likely the patients who will be unable to maintain the healing of the esophageal lining, without staying on their PPI.

The following discussion will expand on "lifestyle issues", and then our current approach to drugs, mostly PPI therapy.

Lifestyle factors

- A leading cause for worsening reflux, or the only cause for reflux in a few patients, is obesity, or recent weight gain. In these patients, there can be significant improvement in reflux symptoms, and also in the severity of reflux esophagitis, with even fairly modest weight loss.
- A second cause for worsening reflux, is cigarette smoking. The act of inhaling, and the effect of many compounds in cigarette smoke, including but not restricted to nicotine, seems to increase the exposure of acid to the lower esophagus, and may also interfere with the defence and healing mechanisms of the esophageal lining.
- A third cause relates to the timing of meals, and the amount consumed at mealtime. Reflux is improved (reduced) by eating small regular meals. The current habit, which seems common, (and possibly more common in reflux patients) of skipping breakfast, is bad for control of reflux. There is some research suggesting that skipping breakfast also contributes to more difficulty in controlling weight, but weight is a very complex and controversial topic.
- Concerning the timing of meals, the most important thing is to avoid lying down after meals, and equally avoid eating, especially large meals, or even large amounts of liquids, before bedtime. We ask patients to avoid eating or drinking anything for 2-3 hours before bedtime, and this includes water, which is healthy for everybody, except reflux patients in the last 2-3 hours before they go to bed.
- A fourth cause of reflux symptoms is clearly related to certain foods. I consider foods and certain drinks in two categories:
    - The first category consists of foods and drinks that irritate erosive esophagitis, and exacerbate the inflammation, but if we could heal the inflammation, by reducing the amount of reflux, these foods and drinks might be tolerated, and do not need to be

completely avoided. This involves citrus products, tomatoes, onions, and spicy foods, and moderate amounts of alcohol, especially wine, but also hard liquor.

- The second category of foods and drinks are those that seem to affect the lower esophageal sphincter pressure directly, and therefore cause reflux to occur. This category includes alcohol as well (especially excess), and also coffee, caffeine, chocolate, peppermint and spearmint, and fatty food. For this reason, we recommend moderation in these things, i.e. avoiding excess. I personally do not recommend avoiding these things completely, and would prefer that patients to be able to drink some coffee if they wish. The definition of excess is usually more than 2 or 3 (coffee, caffeinated drinks, alcohol), but certainly the more of these things that can be avoided, the easier the reflux might be to control. Coffee seems to exacerbate reflux, and causes it in some patients, and unfortunately this includes decaffeinated coffee. On the other hand, caffeine is also harmful, and we advise avoiding excess intake of tea, cola products (Pepsi and Coke), Mountain Dew, energy drinks, and Dr Pepper.
- Unfortunately, some reflux patients seem very sensitive to chocolate, mints, or fatty food. It is generally a patient's choice, whether he or she would like to work even harder on dietary issues, or continue to take small amounts of these things, and in addition, if and when necessary, take medication.

- Another factor that helps some patients, especially those with more problems at night, or possibly with nocturnal regurgitation, would include elevation of the head of the bed, however this can be technically difficult, and is not usually very effective. Contrary to advice which I saw on the Internet, it is not useful to use a couple of extra pillows, and we would prefer to see the entire bed on a slant of 10-15°, using blocks under the head of the bed, or a Bedge™.

Medication for heartburn

Many patients will use antacids such as TUMS, Rolaids, Gaviscon or Maalox. This is fine if the disease is well-controlled, and if the patient has either no evidence of erosive esophagitis (which can only be proven by endoscopy), or is a patient who is at very low risk of erosive esophagitis, or esophageal cancer. The risk factors for erosive esophagitis and esophageal cancer include male gender, age over 40, obesity, smoking, alcohol excess, and long-standing symptomatic acid reflux. Unfortunately, risk factors are only a guide, and we are concerned that some patients have very few, if any, symptoms of reflux, but seem to have underlying GERD, and some of them have underlying esophagitis and appear to be at risk for esophageal cancer.

H2 blockers (such as Zantac or ranitidine, Pepcid or famotidine, and several others, such as Tagamet or cimetidine, which is very old and no longer prescribed) appear to be very effective at relieving GERD symptoms, but do not heal erosive esophagitis nearly as well as PPIs. They continue to be available, both over-the-counter, and at higher doses, by prescription. There was a recent concern about certain brands or formulations of ranitidine, and it was withdrawn from the market for a time.

PPIs (proton pump inhibitors)

This group of drugs, which began with Losec (omeprazole) , and now includes Nexium (esomeprazole), Tecta (pantoprazole), Pantoloc (also pantoprazole), Dexilant (dexlansoprazole), Pariet (rabeprazole), and several others, are potent suppressors of acid production.

These drugs effectively heal reflux esophagitis, although they sometimes have to be taken twice daily. In almost all cases, they work best when taken 15-30 minutes before meals. Dexilant is an exception, because of a special chemical property, that seems to allow the drug to be effective no matter what its relationship to mealtime, and also longer-acting.

PPI's are also used to treat, heal, and prevent peptic ulcer disease and other causes of bleeding from esophagus, stomach and duodenum, and much of the evidence for long-term PPI use, and the evidence for safety of that use, comes from studies where the alternative would be potentially upper GI bleeding and/or even death. Obviously GERD does not represent quite such a dramatic risk/benefit ratio, but other patients on PPI therapy may not be able to stop them safely. Many patients with GERD are unable to stop them without developing recurrent reflux symptoms.

I would like to address a couple of issues which are highlighted on the Internet as major concerns, according to various alternative or "integrative"/complementary practitioners. I will give you our standard medical advice, because we are very aware of potential problems with these drugs, and we certainly do not want people on these drugs longer than necessary, or on them at all, if there are reasonable alternatives.

Before I launch into a more detailed discussion about the use and potential side effects of this class of drugs, I would like to make a disclaimer. I do not do, and never did, research on these drugs, and I have not received any payment from any drug company, in more than 15 years, (even then, I was only briefly funded to attend a meeting of similar specialists, to advise a particular company on our expert opinion as to the use and marketing of their reflux product). I no longer partake in such exercises, and in addition, I refuse to meet with pharmaceutical representatives (reps) in my office, or in restaurants. I am acutely aware of the effects, both desired and undesired, of such interactions between pharmaceutical reps and physicians.

In addition, practicing physicians, including specialists, take the duty and privilege to prescribe very seriously. We are very careful to adhere to ethical principles, and most importantly to do no harm, and to consider carefully the "risk/benefit" ratio for any intervention, whether it be a prescription, a diagnostic test, or a procedure.

In 2012, a number of issues were identified and advertised (by the American Board of Internal Medicine, see "Choosing Wisely", at www.choosingwisely.org, and by a Canadian group as well, http://www.choosingwiselycanada.org/recommendations/gastroenterology-2/) as issues to be discussed between physicians and patients, in order to improve care, and eliminate unnecessary treatments, tests and procedures. These experts have also discussed the concept of "deprescribing", which is an important function for physicians, equally if not more important as prescribing.

This group of recommendations includes one on "treating heartburn and GERD", and this list, which includes many other health issues related and also unrelated to gastroenterology, has been updated in November of 2021.

Gastroenterologists are very aware of potential side effects of PPI drugs, in particular related to reducing levels of gastric acid, and how this might affect absorption of certain nutrients, and also the barrier function of gastric acid in preventing certain infections.

Currently, (and in contrast to what is stated on many "alternative" internet sites), there is no clear evidence that PPI use leads to clinically significant malabsorption, or low levels of iron, B12, magnesium, or calcium. Despite the absence of any evidence for harm, I currently recommend (unlike many other GI specialists, who do not think this is useful), in my consultations and reports to family doctors, that the patient on long-term PPI therapy should have **annual blood tests looking at iron, B12, magnesium, and creatinine levels**. We are aware that acid is involved in absorption of iron, and B12, and levels may be reduced in patients on PPI treatment, but we have no strong evidence that supplementation is required, or that clinically significant disease has occurred as a result of PPI's.

Magnesium levels may not be solely related to absorption, as the PPI may affect kidney and even colonic handling of magnesium. We are aware that there are patients who seem to have presented with very low levels of magnesium, with clinical significance, often affecting muscle or heart function, and this may be related to ongoing, or recently prescribed, PPI therapy. It appears to be rare.

I recommend monitoring **creatinine level (annually)** because of the possibility of very rare cases of kidney damage, specifically interstitial nephritis. Nevertheless, there is no current recommendation, from expert specialist societies (in Canada or USA), that creatinine should be monitored. This issue was raised again in the press in February 2016 – see below.

Concerning calcium, we are aware that calcium absorption is related to gastric acid production and secretion. There is currently intense debate, and ongoing research, as to whether PPIs are associated with significant reductions in bone calcium concentrations, or secondly, whether or not PPIs are associated with clinically significant disease such as osteoporosis or osteoporotic fractures. The current recommendations are that **calcium intake should be generous, and probably supplemented**, if a patient is on long-term PPI therapy. Recent research suggests however that PPIs do not cause significant reduction in bone density, nor increased frequency of fractures.

Concerning **infectious risk**, there are 2 areas of interest related to PPI therapy, the first being increased risk for pneumonia, and the second being increased risk for gastrointestinal infection, which covers infectious diarrhea, and in particular C. difficile infection.

Currently, the evidence that PPI therapy is a cause for **increased risk of pneumonia** is weak. Association is not evidence of causality. This area continues to be studied over time. Unfortunately, chronic reflux is probably a risk for aspiration (esophageal or gastric contents entering the respiratory tract) pneumonia, and we are also aware that PPI therapy is associated with bacterial overgrowth or colonization of the stomach lining, so that the aspirated gastric juice may be more likely to be infected.

Secondly, there is a proposed and poorly understood effect of PPIs on immune function. However, at this time, PPI therapy is not thought to be a cause of significant immunosuppression in the vast majority of patients.

Gastric acid is a barrier against infection, especially related to food poisoning and traveler's diarrhea, both of which are clearly related to contamination of food or drink (fecal-oral transmission). There is a recognized **increase in the risk of food poisoning and traveler's diarrhea** in patients taking PPI's, however it is very difficult to discontinue PPI's immediately before a trip, especially since reflux is sometimes worse shortly after discontinuing PPI therapy (see the paragraph further down on discontinuing PPI therapy).

Although not clearly understood, PPI therapy appears also to be a risk factor for **C. difficile infection**. The strength of this association is significantly less than the association, and biological plausibility, of antibiotics causing C. difficile infection. Physicians who prescribe PPI therapy are aware of the increased risk for C. difficile, in particular in certain patients such as the elderly, and/or immunocompromised, and/or hospitalized patients, especially those requiring antibiotics.

Finally, there were concerns that PPI therapy (especially, and probably only, omeprazole) would interact with the blood thinning effect of drugs such as Plavix (clopidogrel), but these concerns have largely disappeared. Feel free to ask your cardiologist, or your gastroenterologist, what the latest situation is, if you are being asked to take both drugs.

Like many, or most areas in medicine, reports come out occasionally with findings in the opposite direction from what is currently considered to be "established", and if enough reports of sufficient strength are published, eventually science will change what is "established".

Update added February 2016:

3 areas of potential concern with PPI's were described in mid-2015 and early 2016:

1)A study by Shah NH and colleagues published in PLOS One, June 2015, suggested an increased risk for heart disease in patients on PPI's. This study has many weaknesses, and is a large-scale "data-mining" exercise, showing a possible slight increase, 16% for heart attack, and possibly 50% for cardiac death, but with no evidence for a dose-response, ie higher risk with higher dose, or longer duration. No effect was seen for 2 of the five drugs studied.

2)A study by Gomm W and colleagues, in JAMA Neurology, February, 2016, suggested a possible increased risk for developing dementia in patients on PPI's. This was a pharmacoepidemiological claims data analysis, which is a very weak tool to explore such relationships.

Over 218,000 patients over 75 yrs old in 2004 were studied, but 145,000 were excluded for various reasons. The remaining 74,000 were observed, and 29,500 developed dementia. The risk was increased 44% in regular PPI users. The PPI users were more likely female, older, diagnosed with depression,

stroke, or polypharmacy, each of which was an independent risk factor for dementia itself. Increased age was a risk factor, yet PPI had less effect in older groups (over 85, and 80-84) compared to the effect in 75-79 yr old group.

These 2 studies are known as data-dredging, or at most, hypothesis-generating.

3)A study by Lazarus and colleagues, in JAMA Internal Medicine, January 2016, suggested an increased risk of developing chronic kidney disease linked to PPI's.

10482 patients were collected from 1996-1999, and studied until 2011. The hazard ratio for developing chronic kidney disease was 45%. The patients on PPI's were more likely white, obese, and on blood pressure medication, each a risk factor for CKD itself. The study was then replicated in 248,000 patients in a different State. The risk in nonusers was 1.1 per 100 person-years, and 1.83 per 100 person years, and in PPI users rose to 1.2, and 2.01 per 100 person years, or in other words, 1-2 extra cases per thousand person-years. There was an additional risk for acute (more sudden) kidney injury.

I do recommend annual bloodwork which should include creatinine (a measure of kidney function). It remains unclear whether the main risk is shortly after starting these drugs, or after having been on these drugs for a significant time period.

All three of these studies seem to suggest that the population of patients who take PPI's is likely at slightly increased risk for dementia, heart disease and kidney disease – not necessarily because they take PPI, but because the need for PPI may identify a sicker group, and the PPI may co-exist with other factors which drive the increased risk for disease development. Based on much more solid evidence, if those patients who are on PPI for good reason (often on blood thinners, with increased risk for ulcers or esophagitis, or all three factors) were taken off the PPI, they would have bleeding, and potentially fatal bleeding, at a significantly higher rate than the described rate of dementia, heart disease or kidney disease.

<u>Getting off your PPI</u>

Patients who have Barrett's esophagus are recommended, at this time to stay on PPI therapy indefinitely. Although there is no proof that cancer is prevented, there is good reason to believe that continuous acid suppression could be associated with a reduced risk of cancer, and there is some weak evidence that intermittent therapy may actually cause an increased risk, due to the cycling between healing and injury.

Patients who have erosive esophagitis are thought to be at higher risk for relapse of either symptoms, or silent disease (that could be a potential risk factor for malignancy), when they stop PPI therapy.

Nevertheless, we would like to see all patients, except those with proven Barrett's, to try at least once to get off PPI therapy, and to determine whether or not symptoms are recurrent. In some cases, we might need endoscopy to determine whether or not erosive esophagitis recurs, even if symptoms do not

recur. Unless there have been significant changes in lifestyle, such as significant weight-loss, cessation of smoking, I do not recommend annual attempts at withdrawing PPI.

We are well aware of a phenomenon called "rebound hyperacidity", which is the reaction of the body, and the stomach specifically, to produce even more acid than previously, within about 48 hours of stopping PPI therapy. To try and combat this, I recommend reducing the PPI down to once daily for 14 days before further reduction. In order to reduce from once daily, I recommend going to one pill every second day for six days (3 pills) and then trying to stop. Obviously, lifestyle measures may need to be addressed more aggressively, at this time.

Surgery for GERD

Anti-reflux surgery has been available for several decades and is now performed laparoscopically.

The most common operation is a (Nissen) fundoplication. (There is ongoing research into endoscopic treatments for reflux, but these remain experimental, in my opinion, at this time).

There is good evidence that surgery can be equally effective as, and in some studies more effective than, long-term medication. Surgery is particularly effective in patents who do respond well to PPI medication, and it also very useful, in reducing regurgitation, when this persists, even with medical therapy, but there is no more heartburn. Surgery is an option for patients who cannot take PPI's due to side-effects, those who will not take pills for reasons of personal philosophy, and for those who cannot afford long-term medication. There is no evidence that surgery can prevent long-term complications of reflux, including cancer.

The latest, and in my opinion exciting, advance in the surgical treatment of reflux disease would be the magnetic bracelet, LINX™, system. This was been FDA approved back in 2017 or 2018, in the States, and some medium-term results have been published, and presented at conferences, but the device has not yet been approved by Health Canada. Unfortunately by 2021, this technology is still not released in Canada, and there may be concerns for durability with longer-term studies in US,

My main concern about surgery is that some studies suggest that the "tightening" can loosen after some years. One study suggested that 50% of surgical patients were back on anti-reflux medications at 10 years. My second concern is that if there is any trouble swallowing, before surgery, surgery may make this worse, often temporarily, but sometimes for long-term, and that trouble swallowing is difficult to treat. There can be other side-effects with surgery, even if everything goes well. In my opinion, surgery should not be done because people fear side-effects of long-term medication. The PPI's are one of the safest class of drugs, and have been prescribed for more than 20 years, with only infrequent and partially understood short-term or long-term serious adverse effects.

Good luck with your reflux disease. Please ask your family doctor, or myself, if you need further clarification.

See next page for a review of the CTV story of May 2019….

Update (May 2019):

In 2019, a short TV story appeared and adjacent Internet article from CTV was entitled "**Millions of Canadians using acid reflux drugs for too long, risking health side effects**".

https://www.ctvnews.ca/health/millions-of-canadians-using-acid-reflux-drugs-for-too-long-risking-health-side-effects-1.4409011

This article was widely circulated on Facebook.

In my opinion, this article was poorly written, unbalanced, and poorly researched, without any evidence that they spoke to gastroenterologists, who prescribe these drugs frequently, and take the prescribing of them, and the potential side effects, very seriously. Doctors in general, and specialists in particular, routinely consider risks, benefits and alternatives in all cases of treatment including prescriptions, over-the-counter medications, herbal products, surgery, and many other treatment modalities.

If you read this article, (and several patients asked to discuss this with me), I draw your attention to the following issues:

1) The "recommended two-month period" does not apply to specialist prescriptions.

2) the comment that up to 70% (of Canadian seniors) are taking the pills over long-term, is confusing, and should state that up to 70% of the Canadian seniors who are taking the pills, seem to be using them on a long-term basis. Whether or not this is "inappropriate" is highly controversial.

3) the statement that "the side effects associated with taking proton pump inhibitors over the long-term include an increased risk of bone fractures, an inability to absorb nutrients, kidney damage, stomach infections and even a high risk of dementia" is very wrong, very misleading, and raises a number of complex issues.

4)The most important (issue) is that **"side effects associated with… any drug" do NOT necessarily mean, in medicine or science, that those side effects are caused by the drug.**

5) Almost equally importantly, recent literature and research suggests that PPIs do not cause an increased risk of bone fracture, and inability to absorb nutrients, stomach infections, or dementia. There is no doubt that the PPIs can on rare occasions be associated with kidney damage and probably cause kidney damage in rare cases (we have known about this for several years, and this is not really "news", especially in 2019).

The comment that "other medications with less dangerous side effects can be prescribed…" suggest that PPIs have dangerous side effects, which is actually true for all drugs, but needs to be considered in terms of the frequency. In fact, PPIs are one of the safest classes of drugs prescribed. The very large number of Canadians taking these drugs for long periods (which was the headline of the article) is actually proof of the safety even if some of those Canadians should come off those drugs, or try and replace the drugs with other weaker drugs such as H2 blockers.

Finally, the last two paragraphs suggesting dietary and lifestyle factors to “prevent heartburn without a proton pump inhibitor” imply that doctors do not mention these treatments, but they are obviously addressed in detail earlier in this paper. Ironically, there is very little published evidence confirming the effectiveness of these dietary and lifestyle recommendations, but we believe strongly that they should be discussed in detail with every patient who is on a PPI.

I hope this helps you to recognize the need for a balanced approach. I did write to the author and had some discussions. I pointed out that in fact a very great number of patients are taking these drugs, not for heartburn or indigestion, but actually to protect the lining of the stomach and the esophagus against bleeding, and precancerous situations such as Barrett’s.

As stated previously, and essentially well-known, gastroenterologists recommend that PPI therapy should be reviewed, discussed, and alternatives researched, at least every 1-2 years, BUT patients should not stop the PPI without speaking to the prescribing physician. It is my impression that some pharmacists are now advising patients that they should consider getting off these “dangerous drugs”, but responsible pharmacists would suggest that a patient discuss this prescription with their doctor.