



Eosinophilic Gastrointestinal Disease

Eosinophils (e-o-sin-o-fills) are a type of white blood cell that circulate in the blood and are a normal part of the immune system. When triggered by allergies or infection, eosinophils increase in number and become active. In the short-term, this response is important and effective in clearing the body of pathogens. Certain tissues and organs throughout the body are accustomed to eosinophils, including some parts of the gastrointestinal (GI) tract. However, a disease state can occur when eosinophils are present in areas where they don't normally occur on an ongoing basis, resulting in chronic inflammation. This prolonged tissue infiltration and inflammation can ultimately affect the function of that organ.

In recent years, physicians have been diagnosing a rare condition of unknown cause, called eosinophilic gastrointestinal disease (EGID), with increasing frequency in children and adults. EGID is characterized by chronic inflammation in the gastrointestinal (GI) tract caused by a greater than normal number of eosinophils without evidence of other causes (e.g., infections, allergy).

Physicians classify the disease according to the body tissue where the eosinophils accumulate. Each type of the disease requires monitoring. There is currently no cure for EGID.

- **eosinophilic esophagitis** (EoE) is the most common type of EGID, in which large numbers of eosinophils are found in the esophagus, where normally there are no eosinophils. The esophagus is the tube that carries food from the mouth to the stomach.
- **eosinophilic gastroenteritis** (EG) affects the stomach and/or the small intestine.
- **eosinophilic colitis** (EC) is the rarest form of the disease and describes the occurrence of high levels of eosinophils in the large intestine.

EGID can affect people of all ages and ethnic backgrounds, although there appears to be associated sex and genetic factors. Research has found that 75% of individuals with EoE are male and 70-80% have other disorders such as asthma, eczema, and seasonal and/or food allergies. Most of the literature is based on EoE and the evidence base for interventions for EG and/or EC is poor and often adapted from EoE studies. Despite the advances in EoE familiarity and diagnostic criteria, there are likely many people living with EoE who are currently undiagnosed.

Symptoms/Diagnosis

Having too many eosinophils in the esophagus causes inflammation that makes swallowing difficult. The symptoms vary for each person and can include difficulty swallowing solids (often meats, rice, drier foods like bread), a feeling of food getting stuck after eating, vomiting, reflux, heartburn, pain on swallowing, and abdominal and/or chest pain. Many patients have adapted and learned to cope with their disease by modifying their eating behaviours (avoiding certain food that may trigger symptoms, avoiding eating out in restaurants, etc.). This can lead to isolation, fear, and social anxiety and can seriously restrict quality of life.

Younger children might present with poor growth, vomiting, food refusal, and difficulties transitioning to more solid foods. Left untreated, EoE is usually associated with persistence of symptoms and inflammation and can progress to permanent damage to the esophagus by scarring and stricture formation (narrowing of the esophagus). This can result in a prolonged obstruction of the esophagus where food can get stuck (food bolus impaction) and needs removal by means of an emergency procedure. The disease course of EoE is chronic in most, if not all, patients with persistence of symptoms and esophageal

The acronym 'IMPACT' identifies these adaptive behaviours:

- Ingest fluids with meals
- Modify food (cutting into small pieces, pureeing)
- Prolong meal times
- Avoid hard texture foods
- Chew excessively
- Turn away tablets/pills

eosinophilia if not treated properly. Quality of life can be improved with effective therapy.

Symptoms of EG are even more non-specific but may include diarrhea, abdominal pain, bloating, early satiety, swelling (edema), and/or iron deficiency anemia. Symptoms of EC typically involve bloody stools and diarrhea.

Unfortunately, many individuals with EGID can go for years without a proper diagnosis, as the symptoms of EoE are similar to other well-known GI diseases such as gastroesophageal reflux disease (GERD), EG can resemble symptoms of functional dyspepsia, and the symptoms of EC are similar to Crohn's disease, ulcerative colitis, and celiac disease. EGID is a relatively newer condition that has less general awareness and the diagnosis is not always straight forward. You should not initiate treatment prior to consultation with a gastroenterologist, who can diagnose these conditions.

At present, the only way to diagnose EGID is through biopsies from an endoscopy and/or colonoscopy. During an endoscopy, a physician inserts a flexible tube with a light and a tiny camera at the end (an endoscope) through the mouth to examine the esophagus, stomach, and first part of the small intestine. For a colonoscopy, a physician uses a long, flexible tube (a colonoscope) inserted via the anus to view inside the colon. For a biopsy, the physician extracts a tiny piece of tissue for examination under a high-powered microscope. A pathologist reviewing biopsy samples will look for characteristic features of EGID but will also count the number of eosinophils. The combination of relevant symptoms and a high eosinophil count will lead to a diagnosis of EGID.

Treatment

Treatment will vary depending on the part of the GI system affected, but typically includes medication and adjustments to diet after a comprehensive review with your gastroenterologist. The multidisciplinary input of a dietitian and an allergist are often required to optimize management. The goal of treatment is to reduce symptoms as well as demonstrate improved

endoscopic and histologic appearance, which means a reduction and ideally an elimination of the volume of eosinophils in the affected tissue. The treatments do have to be individualized, as what works for one person might not work for the next.

In EoE, long-term treatment is required. If therapies are discontinued, as with other chronic diseases, the inflammation commonly flares up after a few months.

Dietary Therapy

Dietary therapy is one of the primary treatment methods. These can be effective whether or not you have a previously diagnosed allergic type condition.

While not intuitive, eliminating the most common food allergens is more effective than getting tested and removing foods based on the testing (called targeted elimination). The main reason for this is the testing used is designed for identifying immediate allergic reactions (IgE-mediated reaction), but allergy testing carries very low yield in management of EGID, and is not routinely recommended.

A variety of dietary therapy options are available. There are six food categories that make up the most common allergens: dairy, wheat, eggs, soy, peanuts/nuts, and fish/shellfish (and rarely beans). Aeroallergens have also been implicated in a minor group of patients with EGID.

Previous recommendations involved removing all six food groups and adding back foods stepwise if the diet is effective (after biopsy review), but evidence shows that starting with fewer may be sufficient and more sustainable. However, it is important to note that you must eliminate the foods for quite some time, typically 8 weeks, to know whether it is effective. Some sets eliminate single food groups such as dairy, or wheat as the first intervention. Another approach has been called the 2-4-6 step-up elimination diet. Step-up therapy involves removing the two most allergenic foods (dairy and wheat), then, if that is not sufficient, removing the four most allergenic (dairy, wheat, eggs, and soy), and if that is still not providing relief, removing all six.

While there isn't a perfect way to do the eliminations, trial of food elimination followed by endoscopy and biopsies are a must.

The most effective dietary approach is an elemental diet, which involves only drinking a specialized balanced formula that has no intact proteins. This option is restrictive and difficult to follow because it involves receiving nutrition from an amino acid formula instead of eating food. Most individuals would require a feeding tube, as the taste of the formula is unpleasant. It is also extremely expensive. Elemental therapy is not meant to be a long-term treatment and is done under exceptional circumstances.

While dietary approaches may be appealing because they

potentially offer effective treatment without medication, they also require massive restrictions on daily food choices and may impact quality of life. There are also important factors, such as affordability and cost, which those affected by EGID need to consider. Physicians do not recommend eliminating foods beyond the six food groups stated above, as this could result in poor nutrition. Being unable to afford to see a dietitian, or having to pay for the elemental diet formula, might be financially difficult, depending on your healthcare plan.

Dietitian counselling services in Canada can quickly become a huge cost to individuals who need ongoing advice. As the number of individuals with this disease continues to increase, it will be important to address the access issues to publicly-funded dietitian support to ensure patients are receiving adequate nutrition. Provincial governments should also reconsider their eligibility criteria for public coverage of all medically therapeutic formulas, such as elemental formula. For example, individuals living in Ontario aren't eligible for this coverage if they are able to tolerate some solid food.

Medication

Budesonide (Jorveza™) is the only medication approved by Health Canada to treat eosinophilic esophagitis in adults. It is not approved for children at this time. Jorveza is an orodispersible tablet which must be placed on the tip of your tongue, then pressed into the roof of your mouth, allowing it to slowly dissolve. This method of administration allows the medication to work locally in the esophagus to reduce the volume of eosinophils. The undissolved tablet must not be chewed or swallowed. Treatment involves taking one tablet twice daily. The usual duration of the induction treatment is 6 weeks and may be extended if needed. Then, maintenance therapy duration is determined by the treating physician. To ensure that your medicine works properly, always use it as described in the instructions for administration.

Before Jorveza™ was approved, many physicians prescribed other swallowed (topical) corticosteroids to treat EoE. Some individuals might still be taking these medications, especially children. These include fluticasone (Flovent®) and budesonide (Pulmicort®). Individuals administer Flovent® via a metered-dose inhaler, by puffing the medication into the mouth and then swallowing. For those using Pulmicort®, a pharmacist can mix it for you, otherwise you can mix it at home. Typically, you open a small, sealed container (ampoule) of the drug and mix it with multiple packages of a sugar substitute, such as Splenda®, and then swallow it. Alternatives to Splenda® have been demonstrated helpful, including Neocate® Nutra, a hypoallergenic nutritional supplement more commonly found in food products such as apple sauce, honey, or maple syrup.

Oral thrush is a common side effect of swallowed corticosteroids, so check with your doctor or pharmacist for proper counselling. For the medication to have greatest effect, it is important to not eat or drink, brush your teeth, or rinse your mouth for at least thirty minutes after taking the medication.

For some individuals with EoE, proton pump inhibitors (PPIs) such as omeprazole (Losec®), lansoprazole (Prevacid®), pantoprazole sodium (Pantoloc®), esomeprazole (Nexium®), rabeprazole (Pariet®), pantoprazole magnesium (Tecta®), and dexlansoprazole (Dexilant®) can also be effective. In the past, physicians used PPIs to exclude a diagnosis of EoE, as they thought that positive response to PPIs meant that symptoms were a result of gastroesophageal reflux disease (GERD) rather than EoE. However, new research shows that PPIs might also treat EoE. There are multiple potential mechanisms for this, including anti-inflammatory effects from PPIs or reduced esophageal damage in those who have both GERD and EoE. While these drugs are approved for the treatment of GERD, they are not indicated specifically for the treatment of EoE.

Other medications that have been less studied, such as antihistamines (e.g., ketotifen), which are used frequently for conditions such as hay fever, asthma, and eczema, have also been used to help relieve the symptoms of EGID by stopping the body from reacting to allergens. Montelukast (leukotriene receptor antagonist) has also been used in patients with EGID. There are emerging new agents down the pipeline, such as dupilumab (Dupixent®) for use in patients with severe EoE, and it is already approved for severe asthma, dermatitis, and chronic rhinosinusitis, which could co-exist with EoE.

Whether an individual can control the disease through diet and/or medication, it is important to note that symptoms frequently return after discontinuing treatment. There is no right or wrong with regard to choosing medication vs. dietary elimination and your personal input is important.

Outlook

Ongoing care for individuals with EGID is required, including the likelihood of additional endoscopies to assess how the digestive tract is responding to specific treatment. Untreated EGID may lead to malnutrition, poor growth, and anemia. In some individuals, EoE is complicated by the development of narrowing in the esophagus (strictures) and esophageal remodelling that can cause further issues with swallowing difficulty and food bolus obstruction. It is not clear how long EoE must exist before strictures form but generally it occurs gradually with years of uncontrolled inflammation.

The general principle is to control the inflammation to prevent complications such as strictures. If strictures are present and an individual has been on effective treatment

