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Title: Mucosal impedance in eosinophilic esophagitis and the effect of treatment

Co-Principal Investigator: David A. Katzka, MD and Karthik Ravi MD

Co-Investigators: [redacted]

Study Coordinators: [redacted]

Background:

Eosinophilic esophagitis (EoE) is a chronic disease characterized by esophageal eosinophilia leading to inflammation and fibrosis in response to food antigens. One of the presumptions in this disease is that antigen recognition occurs in the esophagus by dendritic cell recognition and generation of a TH2 allergic response. Although it is speculated that the esophageal epithelium increases its permeability to allow for antigen penetration, this is not well proven.

Mucosal impedance reflects the ability of electric current to flow between two sensors while in contact with the epithelium. An increase in current flow is presumably due to an increase in ions and water crossing the membrane, which are good conductors of electricity. Through this technique an overall measure of "leakiness" of the esophageal epithelium is obtained. This increased permeability may reflect epithelial destruction as in erosive esophagitis, a change in epithelium from squamous to columnar as in Barrett's esophagus or in conditions in which there are dilated intercellular spaces as has been observed in both gastroesophageal reflux and eosinophilic esophagitis.

While standard diagnostic evaluation for EoE includes upper endoscopy with esophageal biopsies, assessment of mucosal impedance is not. Recently, a new technology has emerged allowing for direct assessment of mucosal impedance at the time of routine upper endoscopy. Yuksel and colleagues have described use of a 2mm diameter single-channel catheter used during the time of EGD which demonstrated lower mucosal impedance in areas of erosive esophagitis and in the mucosa of patients with nonerosive reflux disease compared to healthy controls.[1] In the same manner, mucosal impedance may be lower in patients with EoE, allowing for submucosal antigen exposure and the characteristic Th2 response.

Hypothesis:

Patient with eosinophilic esophagitis have diminished mucosal impedance, reflecting increased permeability to allergens occurring at least in the esophagus and possibly in the buccal mucosa.

Primary Aim:

1. Assess mucosal impedance in patients with EoE of both the esophageal and buccal mucosa.

Secondary Aim:

2. Changes in mucosal impedance in patients with EoE following treatment

Methods:

Study Design:

Patients referred to the Mayo Clinic Rochester either with an establish or suspected diagnosis of EoE will be identified. Those scheduled for clinically indicated upper endoscopy for esophageal biopsies either for initial diagnosis or activity assessment of EoE will be studied. After investigation of established or suspected EoE, a total of 75 patients with confirmed EoE patients. In addition, patients undergoing clinically indicated upper endoscopy for indications either than gastroesophageal reflux or dysphagia will be studied as controls. A total of 10 control patients will be studied.

Inclusion criteria:

- Adults ages 18-90 undergoing clinically indicated upper endoscopy
- Patients with EoE, defined as dysphagia with histologic finding of greater than or equal to 15 eosinophils per high powered field on esophageal biopsy despite at least 6 weeks of twice daily proton pump inhibitor therapy
- Patients undergoing clinically indicated upper endoscopy for indications other than dysphagia or GERD with normal appearing esophageal mucosa.

Exclusion criteria:

- Medical conditions such as severe heart or lung disease that preclude safe performance of endoscopy
- Patients with conditions known to be associated with esophageal eosinophilia, including Crohn's disease, Churg-Strauss, achalasia, and hypereosinophilic syndrome
- Inability to read due to: Blindness, cognitive dysfunction, or English language illiteracy

Study Flow:

Patient undergoing clinically indicated endoscopy and esophageal biopsies for diagnosis or assessing activity of eosinophilic esophagitis will be identified. In addition, patients undergoing

clinically indicated upper endoscopy for indications other than dysphagia or GERD will be identified:

1. Before commencing the procedure, a baseline impedance will be obtained by asking the patient to hold the end of the probe against his/her buccal mucosa for 1 minute for an initial reading.
2. Clinically indicated endoscopic exam will be completed
3. On withdrawal of the upper endoscope into the esophagus, a 2.13mm mucosal impedance catheter (Figure) will be passed through the channel of the standard upper endoscope.
4. The probe will be placed on the esophageal mucosa 5cm above the gastroesophageal junction for 5 seconds and recordings obtained.
5. In patients with suspected or established EoE in whom clinically indicated esophageal biopsies are indicated, 2 biopsies will then be obtained at this level.
6. The scope will then be withdrawn to 10 and 20 cm above the gastroesophageal junction and the same procedure including biopsies performed respectively.
7. In total, six biopsies will be taken which is part of the guideline recommended protocol for eosinophilic esophagitis for clinical purposes.
8. Biopsies in patients undergoing clinically indicated upper endoscopy for indications other than GERD or dysphagia in whom biopsies are not ordered will undergo the same protocol, except esophageal biopsies will not be obtained.

There is minimal risk associated with this study. Upper endoscopy carries an approximate 1 in 3,000 risk of perforation, bleeding, and infection. As this is a clinically indicated study, there is no increased risk from the standpoint of endoscopy for enrolled patients. The impedance catheter measures only 2.13mm in diameter and is flexible with a blunt end. Given the catheter size and the fact that it is passed with direct endoscopic visualization, risk of complications such as perforation or bleeding are minimized and are essentially no different than standard EGD with esophageal biopsies. In fact, in the initial description of use of this catheter 69 patients were studied with no catheter associated complications were reported.[1] In addition, as impedance recording requires on average 5 seconds per level to complete, the protocol will lengthen the procedure time on average 15 seconds which will not have clinically relevant implications regarding need for conscious sedation and procedure related risk. There are no additional risks to the subject adding the buccal mucosal impedance testing.

Impedance testing

<u>Statistical Analysis:</u>

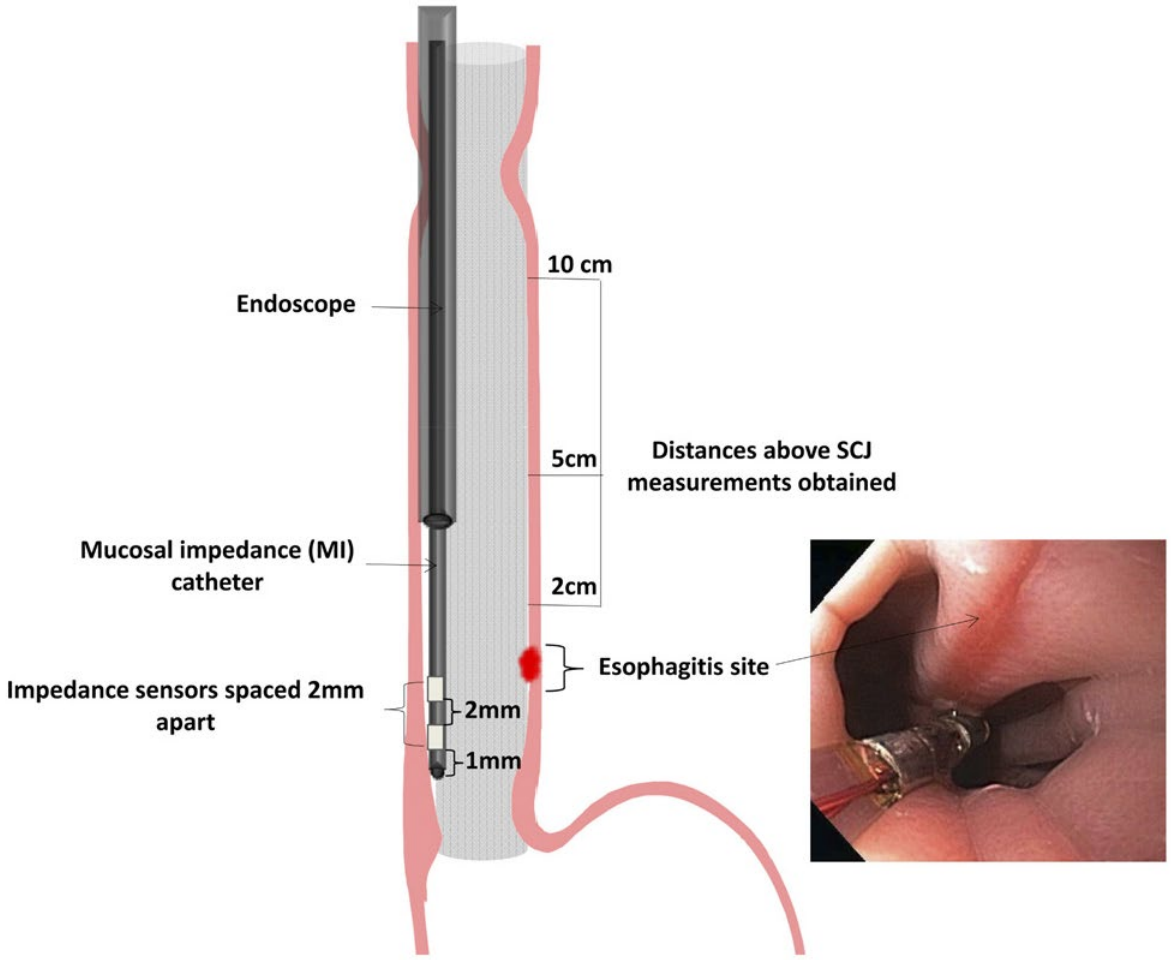
As a pilot, ten patients will be studied before and after treatment for eosinophilic esophagitis. This number of patients will be increased if there are treatment failures until there is a total of ten effectively treated patients studied. Effective treatment is defined by the elimination of esophageal eosinophilia on follow up endoscopic biopsy. Ten control patients without esophageal disease will be studied.

Primary Endpoint:

1. Mean and median mucosal impedance in patients with EoE patients compared to controls

Secondary Endpoints:

2. Maximal mucosal impedance in EoE patients compared to minimal mucosal impedance in control patients to determine a potential diagnostic cutoff value
3. Mean and median mucosal impedance in EoE patients post treatment in comparison to pretreatment



1. Yuksel ES, Higginbotham T, Slaughter JC, Mabary J, Kavitt RT, Garrett CG, Vaezi MF. Use of direct, endoscopic=guided measurements of mucosal impedance in diagnosis of gastroesophageal reflux. Clin Gastroenterol Hepatol 2012;10:1110-3