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PROGRESSIVE ENDOSCOPIC APPROACH TO BALLOON DILATION FOR BENIGN ESOPHAGEAL STRICTURES

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PROGRESSIVE ENDOSCOPIC APPROACH TO BALLOON DILATION FOR BENIGN ESOPHAGEAL STRICTURES

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Behavioral Sciences
at the University of Kentucky

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2022

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ABSTRACT OF DISSERTATION

PROGRESSIVE ENDOSCOPIC APPROACH TO BALLOON DILATION FOR BENIGN ESOPHAGEAL STRICTURES

Benign esophageal strictures are a frequently encountered problem in clinical practice. The management of benign esophageal strictures have slowly evolved over the decades based on "expert opinion." Despite vast amounts of data about the efficacy and safety of dilation, unfortunately there is no consensus on a systematic and safe approach that is efficient, limits complications and provides long lasting improvement of dysphagia. Our group designed a progressive approach to endoscopic balloon dilation based on tailoring certain technical aspects of the dilation process.

Most studies in the literature concluded that endoscopic dilation is safe and effective in relieving dysphagia caused by benign esophageal strictures of various etiologies. There have been few studies that investigated the optimal target of endoscopic dilation of benign esophageal strictures.

Our main retrospective secondary study, 27 patients underwent balloon dilation for benign esophageal stricture. Etiology of the esophageal stricture (n=27) included, peptic (n=18, 66.7%), anastomotic (n=4, 14.8%) eosinophilic esophagitis (n=3, 11.1%), post Heller myotomy (n=1, 3.7%) and radiation induced (n=1, 3.7). The diameter of the esophageal stricture ranged from 6mm to 12mm with the most common diameter being 9mm (15%) or 10mm (26%). Most balloon dilations started at 15mm (range 12-15mm, n=26, 59.2%) or >15mm (n=11, 40.7%) with end dilation of <15mm (n=4, 14.8%), 15-<18mm (n=7, 25.9%), 18-20mm (n=16, 59.3%). Most patients had 1 to 3 dilations at an interval of every 2-4 weeks to achieve goal diameter of 16-8mm. Many patients with follow up data (77%), all had clinical improvement of their dysphagia.

Our study sheds light on the possibility that our novel progressive approach improves the patient's dysphagia without causing complications, although further investigation is warranted in the form of a prospective randomized trial. Although endoscopic esophageal dilation is considered the best initial therapeutic approach for benign esophageal strictures, the best technique to perform the procedure remains to be determined.

KEYWORDS: Endoscopy, Esophageal stricture, Balloon Dilation, Dysphagia

Chad Joseph Cooper, MD, MHA

12/03/2022

Date

PROGRESSIVE ENDOSCOPIC APPROACH TO BALLOON DILATION FOR BENIGN ESOPHAGEAL STRICTURES

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Date

DEDICATION

This work is dedicated to all patients with benign esophageal strictures. Also, to those who participate in research to help advance the field of Gastroenterology.

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CHAPTER 1. INTRODUCTION

1.1 Introduction

Benign esophageal strictures are a frequently encountered problem in clinical practice. Patients with an esophageal stricture typically have dysphagia (difficulty swallowing) to solids and sometimes liquids too. The goal of endoscopic intervention for patients with benign esophageal strictures is relief of dysphagia by disrupting the stricture hence, increasing the diameter of the esophageal lumen by dilation. Dilation is accomplished by application of expansible forces (inflation pressure and dilation force) against the luminal stenosis. No clear advantage of either balloon or mechanical dilation (tapered solid dilation) has been demonstrated but the choice of which to use is provider dependent. Treatment of esophageal strictures with dilation is a relatively safe and effective procedure that has been done for decades.

1.2 Conservative Endoscopic Dilation Approach

For decades, the ‘‘rule of three’’ has been accepted and applied to mechanical dilator (tapered solid dilation) use for esophageal strictures. This conservative approach to dilation was designed to reduce the risk of complications such as bleeding or perforation. The starting point and degree of dilation within a session is based on the severity of the stricture. Specifically, the initial dilator chosen is based on the known or estimated stricture diameter followed by serial increases in dilator diameter. After moderate resistance is encountered with the mechanical type of dilator, no greater than three consecutive dilators in increments of 1 mm should be passed in a single session. However, following this rule increases the number of endoscopic dilations required and the health care-related costs (1).

This rule does not apply to balloon dilators, studies have suggested that inflation of a single large diameter dilator (>15 mm) or incremental dilation of greater than 3 mm is safe in simple esophageal strictures (2). Obviously, perforation remains the concern, although balloon dilation provides real-time, direct visualization of the mechanistic effects of the dilation and allows more aggressive but safe dilation. Although more expensive, balloon dilation seems to result in safe management of more complicated and tighter strictures with fewer sessions and a lower recurrence rate (2). Most providers perform a balloon dilation to a desired lumen diameter and only perform another interval dilation procedure if dysphagia recurs in the future. Most endoscopists are trained to dilate up to a satisfactory luminal diameter based on their discretion once either resistance is felt, or an adequate therapeutic mucosal tear or excessive bleeding is endoscopically visualized.

1.3 Evolution of Endoscopic Dilation

The management of benign esophageal strictures have slowly evolved over the decades based on "expert opinion." For instance, the "rule of three" in dilation of esophageal strictures suggests that in a single session, no more than three bougie dilators of sequentially larger size should be passed once moderate or greater resistance is evident (1). Unfortunately, no meaningful guideline exists to help providers achieve long-lasting dilation free periods of benign esophageal strictures. How much dilation can be achieved in a single endoscopic session of dilation, and what luminal diameter should be the end point remains controversial. There is no data on the optimal duration over which the balloon is inflated. Most would agree that gaining 1 to 2 mm of luminal diameter with three consecutive passes of dilators of increasing size during one session is a good general rule. Most patient experience complete relief of dysphagia when a luminal diameter of >15mm

is achieved. There have been a few recent studies that touch on a single aspect of the balloon dilation technique such as inflation time, interval between balloon dilation sessions, or optimal balloon dilator size. Each of the studies demonstrated an improvement in dysphagia or achieved a durable esophageal lumen after dilation. With our progressive endoscopic approach, we alter not just one but a few technical aspects of the balloon dilation technique process to determine if a larger esophageal lumen diameter of the stricture can be achieved, resulting in better clinical outcomes. Even though our two retrospective studies are not definitive, it does raise the potential that an algorithm for effective balloon dilation of benign esophageal stricture can be achieved with considerable results.

1.4. Progressive Endoscopic Dilation Approach

At our tertiary medical center, we changed a couple of technical aspects of the conservative balloon dilation technique to determine if this would result in a more efficient and safe approach for benign esophageal stricture management. The progressive approach involves gradual inflation of balloon diameter over 3 minutes from the smallest to largest balloon diameter size of that catheter. Depending on the degree of narrowing of the esophageal stricture, the initial balloon diameter chosen was 12mm with the goal of eventually achieving >=16-20mm dilation. Consecutive dilation procedures were scheduled within 2-3 weeks until a target diameter of at >= 16 mm was achieved regardless of symptomatic relief of their dysphagia. At the next endoscopic procedure, the balloon diameter used will be the next size up based on previous session. For example, in the first session a 12-13.5-15mm balloon diameter was used, second session we will use a 15-16-18mm balloon diameter and third session an 18-19-20mm balloon diameter will be used.

1.5 Critical Evaluation of Our Approach

The main concern with our progressive endoscopic dilation approach is if it increases the rate of complications especially perforation or hemorrhage due to our goal of achieving a lumen diameter of >16mm in as few dilations as possible. According to the medical literature there has not been a correlation established between size of balloon dilation and rate of perforation or hemorrhage. The consensus during fellowship training and in medical practice is to not aggressively dilate too much more than the starting diameter of the esophageal stricture. Usually when we observe a tear in the mucosal layer of the stricture after dilation, we tend to stop further dilation due to the fear of perforation or hemorrhage, but this may not be the case. With our progressive dilation approach, a gradual stepwise dilation over 3 minutes allows a controlled dilation without excessive balloon inflation force. The key is to follow the simple tenet "start low and go slow" when performing dilation. We routinely inspect the esophageal lumen mucosa by direct visualization through the balloon after every 1-2mm dilation increments or after encountering resistance.

The other concern is performing a consecutive dilation 2-3 weeks later may accrue excessive healthcare costs and putting the patient through unnecessary endoscopic procedures. Our goal is to start with a 12mm diameter balloon dilator, progress slowly with a repeat dilation session every 2-3 weeks, with the goal of achieving a diameter of 16 to 18 mm. For simple esophageal strictures this can be achieved during the initial endoscopic session, whereas complex or tight strictures may require an average of 2 to 5 endoscopic sessions. By performing another dilation of the stricture at short intervals (every 2-3 weeks) prior to the patient either complaining of recurrent dysphagia or restenosis of the stricture,

may provide a longer lasting effect. We believe this provides longer relief of dysphagia and maintenance of the esophageal lumen prior to recurrent fibrosis of the stricture.

1.6 Significance of Our Research

Even though the conservative endoscopic management of strictures is a safe and effective method for benign esophageal strictures and relief of dysphagia, there may be a better way. The current treatment modality of choice in benign esophageal strictures is endoscopic dilatation, although the best technique for dilatation and type of stricture amenable to treatment is controversial. A variety of endoscopic therapies are available to treat these strictures, although even in the current era there are relatively few prospective and/or randomized studies available to compare different techniques and clinical outcomes, and most of the available literature is based on retrospective data.

Despite vast amounts of data about the theory of how to dilate, unfortunately there is no consensus on a systematic and safe approach that is efficient, limits complications and provides long lasting improvement of dysphagia. Little is known about optimal size of the balloon dilation and inflation time. There is also no consensus regarding how frequent the interval of balloon dilations should be performed. Our study sheds light on the possibility that our novel progressive approach may improve the patient's dysphagia without causing complications, although further investigation is warranted. This study will build onto the current medical knowledge and lead to significantly better endoscopic management of benign esophageal strictures in the field of gastroenterology.

CHAPTER 2. BACKGROUND

2.1 Background

A benign esophageal stricture is an often-encountered problem in gastroenterology, characterized by a narrowing of the esophageal lumen causing dysphagia to solid food and/or liquids. Other symptoms of esophageal stricture include regurgitation or aspiration, chest or epigastric abdominal pain, or weight loss. The formation of benign esophageal strictures is caused by the production of fibrous tissue and deposition of collagen stimulated by chronic inflammation (3-4). The most common causes of benign esophageal strictures are listed in Table 1. These include peptic strictures due to uncontrolled gastroesophageal reflux disease (GERD), anastomotic (post-surgical), radiation induced, ingestion of a caustic substance, or eosinophilic esophagitis (3, 5-6).

2.2 Etiologies of Benign Esophageal Strictures (see Table 1)

Peptic included strictures account for up to 80% of all benign esophageal strictures (7). Peptic injury results from the chronic exposure of the esophagus to gastric acid contents. Fortunately, there has been a decrease in the incidence of peptic strictures due to the widespread use of proton pump inhibitors (PPI's) which help regulate excessive gastric acid production. Schatzki rings are benign, fibrous rings that are commonly found in the lower esophagus and are strongly associated with the presence of a hiatal hernia (8). Caustic strictures are most commonly due to the ingestion of concentrated alkali solutions (lye). Eosinophilic esophagitis is becoming a more frequently encountered cause of benign esophageal strictures. This entity is common in young patients with otherwise unexplained dysphagia that presents with food bolus impaction. Eosinophilic esophagitis is an inflammatory disease of the esophagus due to the infiltration of eosinophils into the mucosal layer. Esophageal strictures are present in 30% to 80% of adults with eosinophilic

esophagitis. Anastomotic strictures can occur after esophagectomy for esophageal cancer resection or other esophageal surgery such as repair of esophageal perforations or thoracic trauma. Anastomotic strictures usually result from ischemia or excessive fibrosis of the anastomosis (esophagogastric) (9).

2.3 Classification of Benign Esophageal Strictures

Benign esophageal strictures are categorized into two types: simple and complex (10). Simple esophageal strictures are short (1-2 cm long), focal, and with a diameter >12mm that allows the passage of the upper endoscopy that has diameter of 9-10mm (10-14). These strictures include Schatzki rings, esophageal webs, and peptic strictures. Simple esophageal strictures typically tolerate large increments of dilation at one session. Complex benign esophageal strictures are usually long (>2 cm), asymmetric, angulated, and severely narrowed or inability to pass the upper endoscope (10-15). Typically, one to three dilations achieve relief of dysphagia in simple strictures. Complex strictures are more difficult to treat and tend to be refractory or to recur despite dilation therapy (10-15).

The cause of recurrent and refractory benign esophageal strictures is thought to be a result of intense fibrogenesis during healing and after the dilation-induced trauma. The underlying pathogenesis varies depending on the distinct types of strictures. For example, peptic strictures develop because of ulceration and inflammation caused by gastroesophageal reflux, while anastomotic strictures are formed because of relative ischemia at the site of anastomosis. The most common etiologies of recurrent and refractory strictures include anastomotic strictures, caustic strictures, and radiation-induced strictures. Caustic injuries and radiation induced strictures have more involvement of deeper layers of the esophageal wall, such as the muscularis propria, that makes a stricture

more complex to treat and increase the risk for perforation (16). Strictures compromising only a superficial esophageal layer such as esophageal webs, Schatzki ring and peptic strictures, respond better to dilation.

According to medical literature a recurrent or refractory stricture usually results from luminal narrowing from scarring or fibrosis in the absence of inflammation. A benign inflammatory esophageal stricture is not considered in the definition since the stricture is unlikely to improve until the inflammation subsides or is treated appropriately. The benign esophageal stricture is labeled refractory when unable to successfully dilation the anatomic problem to a diameter of 14 mm over five sessions at 2-week intervals (4,13). The benign esophageal stricture is recurrent when unable to keep a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (4,13). When strictures are refractory or recurrent, dilation therapy combined with steroid injections, incisional therapy, metal esophageal stent placement, or surgery may need to be considered (17). To prevent stricture recurrence, the injection of steroids into the stricture site following endoscopic dilation has been reported to prevent stricture recurrence (15-21). The mechanism of action has been suggested to be the local inhibition of the inflammatory response, resulting in a reduction of collagen formation (17-23).

2.4 Method and Types of Dilators

The method of esophageal dilation varies depending on the type of dilator used and how it is performed. Dilation is either done with a balloon or mechanical dilator (Maloney or Savary dilators) that are passed through the esophagus with or without the use of a guidewire and with or without the aid of fluoroscopy. The mechanistic action by which the esophageal stricture is dilated also depends on the type of dilator used. Balloon dilators

dilate the stricture lumen by distributing the dilating force radially and simultaneously across the entire length of the stricture. Mechanical dilators deliver both a radial and a longitudinal force across the entire length of the stricture.

Balloon dilators can be passed through-the-scope (TTS) with or without a guidewire depending on the complexity of the stricture. Through-the-scope balloon dilators are designed to pass through the working channel of the upper endoscope with or without wire guidance so that dilatation can be seen. The balloon is made of low-compliance, inflatable, thermoplastic polymers that allow uniform and reproducible expansion to the specified diameter (17). Most balloons allow for sequential expansion to multiple diameters. The balloon size needs to be carefully matched to the size of the stricture. Dilating balloons are expanded by pressure injection of liquid using either water or radio-opaque contrast using a handheld accessory device. Inflation with radio-opaque contrast allows for fluoroscopic visualization. The hydraulic pressure of the balloon is monitored manometrically to gauge the radial expansion force.

The guidewire balloon dilation approach is used when the stricture lumen diameter is too narrow for the endoscope to pass through or when the stricture is long or angulated. In general, complex strictures typically require the use of a guidewire for mechanical dilators or direct visualization with a balloon dilator either endoscopically or under fluoroscopic guidance (24). The balloon dilator should be positioned so that the narrowest part of the stricture is at the center of the balloon. Multistage diameter balloon catheters enable the application of a multistep radial dilation force by gradually increasing the inflation pressure. The dilators are typically inflated with water (or radio-opaque material if performed under fluoroscopy) to pressures that correspond to specific dilation diameters.

The dilation force can is affected by factors such as the inflation pressure, balloon diameter, and severity of stricture (24). An adequate dilation force at the stricture is important in achieving a therapeutic mucosal tear of the stricture, but excessive dilation force can result in adverse events such as perforation.

As mentioned, mechanical dilators include either Maloney dilators that are mercury or tungsten filled bougies passed without the aid of a guidewire or Savary dilators that are wire guided polyvinyl dilators. The Maloney type bougies have a tapered tip and can be passed either blindly or under fluoroscopic control. This type of dilator is used for simple strictures with a diameter of 12-14 mm. The risk of esophageal perforation is higher due to the blind passage of Maloney dilators especially in patients with a large hiatal hernia, a tortuous esophagus, or complex strictures (25-26). The Savary dilators are polyvinyl chloride, cylindrical solid tubes with a central channel to accommodate the guidewire. They are the most widely used ranging from 5-20 mm diameter. Savary dilators are passed over a guidewire that has been positioned with the tip in the gastric antrum with or without fluoroscopic guidance.

2.5 Technical Aspects of Endoscopic Dilation

The extent of dilation to achieve a certain luminal diameter during a single endoscopic session is still controversial. When using mechanical dilators, the rule of three is applied by dilating at least 1 to 2 mm of luminal diameter dilation with through three consecutive passes of dilators of increasing size during one session. This rule of three is applied to help prevent adverse events such as excessive bleeding or perforation. Depending on the type of stricture, balloon dilators may allow even more increase in luminal diameter to be achieved during a session. The main benefit of balloon dilation is

the direct endoscopic visualization of the stricture during dilation that allows more aggressive but safe dilation.

Patients usually require repeated endoscopies to reach a satisfactory luminal diameter. However, the best target diameter of endoscopic dilation of benign esophageal strictures is unknown and therefore an arbitrary measure. When a luminal diameter of 13-15 mm is achieved, most patients can tolerate a regular diet. But to ensure luminal patency, patients are usually dilated to 16–20 mm. The question is whether the additional millimeters past the 16 mm are effective. The degree of dilation within a session should be based on the severity of the stricture by estimating the stricture diameter, followed by serial increases in the diameter of the dilating balloon (9). One to three dilations are needed to relieve dysphagia due to simple strictures, with only 25-35% of patients requiring repeated dilation (12). There is no data on the best duration the balloon should remain inflated, but national and international guidelines recommend inflation times from 30 to 60 seconds (9-10).

2.6 Potential Complications of Dilation

The most common procedural complications with any type of dilator include perforation, bleeding, infection, or aspiration. The most serious complication of esophageal dilation is perforation. Perforation risk varies between 0.1% and 0.4% (27). The risk of perforation is higher in complex strictures compared to simple strictures (28-29). Radiation induced strictures tend to have severe and highest risk of perforation. Perforation after esophageal dilation usually occurs at the site of the stricture (intrathoracic or intraabdominal part of esophagus). This complication should be suspected if severe or persistent chest pain, dyspnea, tachycardia, or fever occurs. A chest radiograph may show

free air from a perforation. Although a normal chest radiograph does not entirely rule out this possibility. Therefore, a water-soluble contrast esophagogram or contrast chest computed tomogram may be necessary (30). In a few select cases, a fully covered metal esophageal stent is effective management of perforations after dilation of benign or malignant esophageal strictures (31-32). Mild bleeding after effective dilation is common and due to mucosal disruption caused by dilation. Rate of significant hemorrhage after dilation has been reported to be 0.4% (33).

CHAPTER 3. REVIEW OF THE LITERATURE

3.1 Safety and Effectiveness of Dilation for Esophageal Strictures

In a study by Drabek J et al. that looked at the effectiveness and complication rate of balloon dilation for management of benign esophageal strictures. Twenty-two patients were diagnosed as having benign esophageal stricture. All patients except two showed immediate improvement: 59% were cured; 18% had at least one recurrence of the stenosis; 9% had improvement but treatment continues; 14% needed other treatment (34). They had two major complications for perforation. They concluded that balloon dilatation was an effective and safe method for treatment of the benign esophageal strictures.

Polese et al, conducted a retrospective study on 95 patients treated by endoscopic dilation (Savary or through the scope (TTS) balloon dilation) without fluoroscopic guidance for benign esophageal strictures. The etiologies were: anastomotic (n=38), post-fundoplication (n=13), caustic (n=14), peptic (n=11), radiation-induced (n=10) and others (n=9) (35). A total of 472 dilation sessions were conducted without any serious complications. Recurrence of dysphagia was found in 33% and 51% of the patients after 2 months and 1 year, respectively. Improvement of dysphagia, the number of sessions, and recurrence were significantly better in the patients with postsurgical stenosis as compared with those affected by caustic, peptic, and radiation-induced strictures.

Mendelson et al. performed a retrospective study of 74 patients with an anastomotic esophageal stricture after esophagectomy that had been dilated over a 5-year period (564 dilations; median follow-up period, 8 months) (36). Patients were dilated with either TTS balloon dilator (57%), Savary dilators (8%) or both (35%). Of the 74 patients, 93% had initial relief of dysphagia. The stricture recurred in 43% of patients, and 69% were

considered refractory (36). There were no major complications in this study. The prevalence of an esophageal stricture after esophagectomy ranges from 9%-48% (37). These benign strictures may develop because of collagen deposition and fibrin production from deep ulceration or chronic inflammation (12, 33). They found that endoscopic dilation was successful in achieving luminal patency, but anastomotic strictures often recur and are refractory.

Pereira-Lima et al, performed 1043 dilation sessions on 153 patients using Savary-Gilliard dilators or Eder-Puestow dilators (12). Dilation sessions were done on a weekly basis until a lumen size of 14-15mm was obtained. Dilation was repeated whenever dysphagia recurred. Stricture etiologies were postsurgical in 80 patients, peptic in 37, caustic in 12, and from other causes in 11 patients. The median maximum diameter of the inserted dilators was 14mm. The median number of sessions required for achieving adequate dilation, together with relief of dysphagia during the follow-up, among patients with peptic stenosis was 3, in comparison to 5 in patients with either caustic or anastomotic strictures. Absence of dysphagia was accomplished in 66.5% of the patients at the end of follow-up. They concluded that endoscopic dilation is safe and effective in relieving dysphagia caused by benign esophageal strictures of varied etiologies, although frequent repeated sessions are necessary due to stricture recurrence.

3.2 Optimal Dilation Diameter

The optimal target of endoscopic dilation of postsurgical esophageal strictures is unknown. Helsema et al, conducted a retrospective study to compare the dilation-free period of patients with benign anastomotic stricture after esophagectomy who underwent balloon or bougie dilation up to 16 mm with patients who were dilated up to 17 or 18 mm.

Eighty-eight patients were dilated up to the largest diameter of 16 mm and 91 patients to a diameter >16 mm. The stricture recurrence rate was 79.5 % in the 16 mm group and 68.1 % in the >16 mm group (38). The overall dilation-free period had a median of 41.5 days and 92 days, respectively. They concluded that endoscopic dilation over 16 mm resulted in a significant prolongation of the dilation-free period in comparison with dilation up to 16 mm in patients with benign anastomotic strictures after esophagectomy. This study concluded that endoscopic dilation over 16 mm resulted in a significant prolongation of the dilation-free period in comparison with dilation up to 16 mm in patients with benign anastomotic strictures after esophagectomy.

Another important question is whether dilation to 16 mm or more is safe and does not increase the risk of esophageal perforation. In the study by Helsema et al, only one of the eight perforations occurred after dilation of 16 mm or more. The overall perforation rate reported in the literature after endoscopic dilation of benign esophageal strictures, varies from 0 to 1.8% (38). Other studies using balloon dilation deemed that dilation over 3 mm per session was safe and feasible. In a study by Park et al. reported that 89% of patients with anastomotic strictures were dilated to maximum balloon size of 20 mm during the initial dilation session with no major complications. (37). In another retrospective study by Yoda et al, balloon dilation sizes of 12-15mm and 15-18 mm diameter were used in patients with severe (<5 mm diameter) and moderate (5-10 mm diameter) strictures, respectively (39). This study reported a perforation rate of 0.3%. A retrospective study by Kim et al, that included patients with esophagojejunal anastomotic strictures with median diameter of 5-6 mm, reported that 66% of their patients were dilated up to 16.5–20mm in one or two sessions, which the occurrence of only one perforation (40). Despite these

studies being conducted in patients with anastomotic esophageal strictures, it does support our goal dilation point of >16mm during the first one to two endoscopic sessions.

Vermeulen et al, performed endoscopic balloon dilation in 751 patients with benign esophageal strictures. The retrospective study aimed to show risk factors for refractory benign esophageal strictures and assess long term clinical outcomes of endoscopic dilation (41). They figured out that endoscopic dilation up to 13 to 15 mm was associated with a higher number of endoscopic dilations sessions than dilation up to 16 to 18 mm. Furthermore, more than 60% of patients with benign esophageal strictures remained free of endoscopic dilation after 1 year of follow-up. Compared with peptic strictures, anastomotic, radiation and caustic strictures were associated with a higher number of endoscopic dilation sessions.

The findings from these studies and others have several implications for clinical practice. First, they demonstrated that dilation up to 16 to 18 mm was associated with less future endoscopic dilations which suggested that endoscopists should consider dilating to at least 16 mm in benign esophageal strictures. These studies also show that noncompliance with the rule of 3 was not associated with esophageal perforation. Further confirming that dilation over 3 mm per session can be safely performed without an increased risk of esophageal perforation (42).

3.3 Balloon Inflation Time

Wallner et al. evaluated the best balloon dilator inflation time for benign esophageal strictures. Even though there are no national or international guidelines, recommended inflation times range from 20 to 60 seconds (43). The aim of their pilot study was to compare the efficacy of 10 seconds balloon dilation inflation time with 2 minutes inflation

time. Dilation was made using a TTS balloon, with 15-18mm or 18-20-mm diameter. Twenty patients with symptomatic strictures were prospectively studied in a randomized fashion. Of the 20 patients evaluated, the 10-second group required an average of 1.4 dilations per patient; the 2-minute group required an average of 1.5 dilations per patient (15). This pilot study concluded that 10 seconds inflation time was as effective as 2 minutes. Although balloon dilatation is the primary treatment for benign dysphagia, information about the optimal inflation time is lacking. Unfortunately, this pilot study only looked at a two inflation times instead of a range of different inflation times to truly determine a difference. Even though this study investigates an important aspect of balloon dilation it was not descriptive on patient demographics such as etiologies or how the balloon dilation was performed.

Wang et al conducted a study to evaluate the inflation duration of endoscopic dilation for benign esophageal strictures after esophageal surgery or endoscopic submucosal dissection. The clinical effects and adverse events were compared among the three groups, 1, 3 and 5 minutes for inflation time of balloon dilation. There was a total of 57 patients, including 21 in the 1-min group, 18 in the 3-min group and 18 in the 5-min group, were included. The stricture recurrence rate was 76.19% in the 1-min group, 55.56% in the 3-min group and 61.11% in the 5-min group (44). The dysphagia-free periods were comparable between the 3- and 5-min groups but were longer than those in the 1-min group. When the dilation duration was longer than 3 min, muscle layer damage occurred in two patients in the 5-min group and in no patients in the other two groups, which indicated that prolonged dilation could destroy the esophageal tissue structure (44). Three minutes was considered a safe and effective dilation duration for benign esophageal strictures after

esophageal surgery or endoscopic submucosal dissection. This study supports our balloon inflation duration of 3 minutes for the progressive endoscopic approach.

3.4 Subsequent Balloon Dilation Interval

In a study by Buyukkarabacak et al. that aimed to evaluate their 16 patients who underwent multiple dilations with the diagnosis of resistant benign esophageal stricture. All patients underwent dilatation with Savary-Gilliard bougie dilators. Following the first dilation performed for dysphagia, 7 patients underwent endoscopy and dilatation 3 to 5 times within 1-week intervals without waiting for the development of dysphagia symptoms. They found that dilatations performed at frequent intervals without waiting for the symptoms of dysphagia can contribute to safer and more effective results in resistant benign esophageal strictures (45). Even though Savary-Gilliard bougie dilators were used instead of balloon dilators, most studies have not shown much difference between the effectiveness of either type of dilator. This study supports our notion that performing a repeat dilation at a shorter interval before the patient complaints of recurrent dysphagia or restenosis of the stricture, may provide longer lasting relief.

3.5 Factors Affecting Dilation Force in Balloon Dilation

Nishikawa et al. conducted a performed an experiment using phantom models to investigate the relationships between inflation pressure, balloon size, and radial dilation force (46). The balloon dilation procedure was performed for each stricture model using three sizes of balloon: 10-11-12 mm, 12-13.5-15 mm, and 15-16.5-18 mm. Each balloon catheter was placed in the 5-mm stricture model and inflated to the three stages of pressure (2, 4, and 6 atm) for each balloon diameter. Their aim was to determine which balloon size should be selected to achieve a specific target diameter.

There was a positive association between inflation pressure and dilation force was observed for each balloon size. The dilation force increased as the inflation pressure increased for all three sizes of balloons assessed. A greater dilation force was applied for larger than for smaller balloons at the same inflation pressure. They compared the dilation force when multiple sizes of balloon were inflated to a certain diameter (12 and 15 mm). When balloons were inflated to the same diameter, the smaller balloon generated significantly greater dilation force than the larger one. When targeting the maximum dilation (15 mm) of a 12-13.5-15 mm balloon and minimum dilation (15 mm) of a 15-16.5-18 mm balloon using the same 5-mm stricture size, the dilation force was higher in the 12-13.5-15 mm balloon compared with the 15-16.5-18 mm balloon. This is probably because a smaller balloon requires more inflation pressure to achieve the same diameter. Using the same stricture size, the dilation force was significantly higher when applying the maximum size of a smaller balloon compared with a larger balloon. An inverse association between stricture size and dilation force was observed in the 12-13.5-15 mm. They also performed other experiments using 3-mm and 7-mm strictures and obtained equivalent results. They compared the dilation force using stricture models of different severity, and we found that the larger dilation force occurred with severe strictures. To perform safe and effective esophageal balloon dilation, the inflation pressure and balloon size should be selected after considering the stricture size and target diameter (46).

CHAPTER 4. RETROSPECTIVE STUDIES

4.1 Specific Aims

Aim 1) To determine if our progressive endoscopic balloon dilation approach will result in better clinical outcomes, defined as symptomatic improvement and less recurrence of dysphagia based on follow up data. Hypothesis: Our progressive endoscopic approach will have significantly better clinical outcomes in terms of symptomatic improvement and less recurrence of dysphagia in patients with benign esophageal strictures.

Aim 2) To evaluate the technical success of our progressive endoscopic approach, in terms of less return visits for repeat endoscopic procedures due to achieving a lumen diameter of at least 16mm. Hypothesis: The progressive approach will be a more technically successful procedure due to less endoscopic procedures to achieve a goal lumen diameter of at least 16mm.

Aim 3) To determine the rate of postoperative procedural related complications, such as bleeding, infection, perforation with the progressive endoscopic approach in the management of benign esophageal strictures. Hypothesis: The progressive endoscopic approach will be associated with fewer postoperative procedural related complications.

4.2 Materials and Methods

Our studies were retrospective, single center, cohort study and were approved by the IRB of University of Kentucky. We performed an electronic search through our endoscopic database and medical records to find patients who underwent upper gastrointestinal endoscopy with dilation therapy for benign esophageal strictures between January 2012 and December 2017 for preliminary study and January 2012 and November

2021 for our secondary study. We excluded any endoscopic balloon dilation performed by another provider besides Dr. Houssam Mardini, since is the only provider that utilizes the progressive balloon dilation approach. We included adult patients (18-99 years old) who received endoscopic balloon dilation by Dr. Houssam Mardini for a benign esophageal stricture. Strict confidentiality and patient's privacy protection was kept throughout the entire data collection process. At the time of the endoscopic procedure, the details of the procedure were explained to the patient and an informed consent was signed.

Other inclusion criteria included patients presenting with dysphagia (difficulty swallowing) due to a benign esophageal stricture due to any of the following etiologies: peptic (sequela of reflux esophagitis), radiation inducted, caustic ingestion, anastomotic stricture (post-surgical), and eosinophilic esophagitis-associated stricture. Exclusion criteria included patients less than 18 years of age, malignant esophageal stricture, stricture found in the gastrointestinal tract other than the esophagus, diagnosis of achalasia and if the patient was pregnant.

4.3 Data Collection

We retrospectively collected the baseline variables from the electronic medical records that are presented in Table 2 and 3. The following variables were also included in the data collection: the number of endoscopies needed to reach the target diameter; largest luminal diameter reached; number of balloon dilations performed and dilation related complications. The stricture diameter was estimated by the endoscopist and based on the size the dilator at which mild resistance was felt during balloon dilation. To decide the location of the stricture, the esophagus was divided into three segments: proximal (<25 cm from the incisors), mid (25–30 cm from the incisors) and distal (>30 cm from the incisors).

4.4 Pre/post operative and Endoscopic Procedure Detail

Although the endoscopic procedures in this study were not standardized because of the retrospective nature of this study, we give a description of how endoscopic dilation was usually performed at our institution. Endoscopic dilation was performed as an outpatient procedure. Patients were asked to fast for at least 6 hours prior to the procedure. Anticoagulants were stopped 2–5 days before the procedure depending on the type of anticoagulant. No routine antibiotic coverage was required. During the informed consent process, patients were informed about any potentials complications from anesthesia or the procedure such as the risk of perforation, bleeding or infection and the possible need for surgery should perforation occur. Patients received either monitor anesthesia care (MAC) sedation using propofol under the supervision of an anesthesia team or conscious sedation using midazolam and/or fentanyl administered by the endoscopist Dr. Houssam Mardini.

Depending on the degree of narrowing of the esophageal stricture, the initial diameter (mm) size of the balloon dilator was chosen with the goal of eventually achieving >=16mm dilation. Patients were dilated up to a satisfactory luminal diameter based on the discretion of the endoscopist once either resistance was met, or an adequate therapeutic mucosal tear was endoscopically visualized. Patients were discharged 1–2 hours after the intervention after tolerating liquid diet under the supervision of the nursing staff and endoscopist. Any consecutive dilation procedures were scheduled within 2-3 weeks until a target diameter of at >= 16 mm was achieved. The final target diameter was an arbitrary measure that mainly depended on the preference of the endoscopist performing the procedure but maintaining safety measures to prevent procedural complications. The

patient was then discharged and instructed to contact the outpatient clinic in case of recurrent dysphagia.

4.5 Statistical Analysis

All results were expressed as mean or percentage. Descriptive statistics such as means, and percentages were used for continuous and categorical data.

4.6 Preliminary Study Results

During the study period, 19 patients who underwent balloon dilation with a diagnosis of benign esophageal stricture were retrospectively reviewed (Table 2). Of these 19 patients, the mean age of 64 (range 27-86 years) and 58% (n=11) males. The etiology of the esophageal stricture was peptic induced (n=14, 73.6%), anastomotic (n=1, 5.3%) eosinophilic esophagitis (n=3, 15.8%), and radiation induced (n=1, 5.3%). The location of the esophageal stricture included, proximal (n=3, 16%), mid (n=4, 21.1%), distal (n=11, 57.9%), and both proximal/distal (n=1, 5%). All the endoscopic procedures with balloon dilation were performed by the same endoscopist (Dr. Houssam Mardini). The balloon dilation was performed over the course of at least 3 minutes or more. Most common diameter (mm) of the esophageal was 9mm (25%) and 10mm (17.8%). Largest balloon dilation used for esophageal stricture 12mm (n=2, 10.5%), 15mm (n=5, 26.3%), 16.5mm (n=1, 5.26%), 18mm (n=7, 36.8%), and 20mm (n=3, 15.7%). The number of balloon dilations done per patient with esophageal stricture include, one (n=9, 47.3%), two (n=5, 26.3%), and three or more (n=5, 26.3%). Most of the balloon dilation in the rest of patients were routinely repeated between 2-4 weeks. Nine of the 10 patients that we have follow up data on had clinical improvement in their symptoms of dysphagia. Of the 1 that did not have clinical improvement, he had a radiation induced stricture which are typically

refractory strictures. Technical success of the procedure was achieved 100% and no complications occurred in any patient. This study shows that our progressive approach achieves symptomatic improvement without an increase in complications, although further investigation is called for.

4.7 Secondary Study Results

During the study period, 27 patients underwent balloon dilation with a diagnosis of benign esophageal stricture. (Table 3). Of these 27 patients, the mean age of 58 (range 22-86 years) and 52% (n=14) males. Etiology of the esophageal stricture (n=27) included, peptic (n=18, 66.7%), anastomotic (n=4, 14.8%) eosinophilic esophagitis (n=3, 11.1%), post Heller myotomy (n=1, 3.7%) and radiation induced (n=1, 3.7%). Location of the esophageal stricture included, proximal (n=3, 11.1%), mid (n=4, 14.8%), and distal (n=20, 74.1%). All the endoscopic procedures with balloon dilation were performed by the same endoscopist (Dr. Houssam Mardini). The balloon dilation was performed over the course of at least 3 minutes or more. The diameter of the esophageal stricture ranged from 6mm to 12mm with the most common diameter being 9mm (15%) or 10mm (26%). Most balloon dilations started at 15mm (range 12-15mm, n=26, 59.2%) or >15mm (n=11, 40.7%) with end dilation of <15mm (n=4, 14.8%), 15-<18mm (n=7, 25.9%), 18-20mm (n=16, 59.3%) (Table 4). Our goal for dilation lumen diameter was 16-18mm. The number of balloon dilations done per patient were usually 1 to 3 times depending on the severity of the stricture. The patients routinely had a balloon dilation performed every 2-4 weeks. Most patients with follow up data (77%), all had clinical improvement of their dysphagia. There was one patient that did not report clinical improvement of dysphagia. On further investigation, she had a severe 6mm diameter peptic stricture. No complications occurred

in any patient. Technical success of the procedure was achieved in all patients throughout all the procedure done.

This study helps confirm that our novel progressive endoscopic balloon dilation approach may lessen the number of endoscopic procedures but also improve dysphagia without an increased risk of procedural complications. Hopefully, our research will stimulate interest in performing further research studies to investigate the role each technical aspects of endoscopic balloon dilation has on benign esophageal strictures. Changing a certain aspect of how the esophageal stricture is dilated may result in better patient outcomes.

CHAPTER 5. DIFFICULTIES IN THE RESEARCH

5.1 Study Limitations

There are limitations to these studies. First, the sample size was small, and the study was retrospective in design at a single tertiary medical center. A larger prospective and randomized controlled trial is needed to further confirm our results. We would suggest conducting these future research studies at a few tertiary medical centers to inform patient recruitment and decrease bias. These factors introduce bias and decrease the study's statistical strength. However, both our retrospective studies demonstrated that balloon dilation for benign esophageal stricture with our proposed technique had a considerable symptomatic improvement in their dysphagia and improvement in the lumen size of the stricture. Even though a goal dilation of at least 16 mm or more was achieved in most patients it is difficult to determine the long-term dilation-free period due to gaps in the data available and limited long term follow up. Most studies seem to stop at 15-16mm lumen diameter, but some studies suggest that increasing the target diameter of endoscopic dilation up to 18-20mm may be more effective.

5.2 Research Difficulties

The original plan for the research study was to be a double-blind, randomized prospective clinical trial of comparative effectiveness of two balloon dilation methods (standard vs. progressive approach) for benign esophageal strictures. We planned to recruit a total of patients 40 that would be randomized using blocks of 8 or 10 to have half of the participants (n = 20) that would have the standard approach of balloon dilation and the other half (n = 20) would have the progressive approach to balloon dilation. This type of research plan would have limited the issues we faced with our retrospective study.

We had originally plan to start the prospective study at the end of 2019 with a few patients that were enrolled but unfortunately the COVID-19 pandemic became a huge obstacle for patient recruitment, enrollment, and performance of elective or non-emergent endoscopic procedures. There were supposed to be other endoscopists that participated in the research study, but they had left the University of Kentucky gastroenterology division prior to or during the time that the study was conducted. Another issue we encountered was that I finished my gastroenterology fellowship at University of Kentucky on June 30, 2018, then went to Maine Medical Center to complete my advanced endoscopy fellowship by June 30, 2019. Afterwards, I accepted a full-time position as a gastroenterologist/advanced endoscopist with Gastroenterology Associates, P.C. in Casper, Wyoming. Due to my absence from the University of Kentucky, I was not able to physically be involved with patient recruitment, enrollment, or data collection process. We had to rely on other students and research personnel to assist with the progress of the study and collect the retrospective data.

Due to the many obstacles, we encountered, the research study was converted into a retrospective study with focus on patients that had underwent our proposed progressive endoscopic dilation approach for benign esophageal strictures by Dr. Houssam Mardini. Converting the research study to retrospective made the data collection and analysis part easier but of course with any retrospective study there is bias, gaps in the data collection and limited statistical strength to make definitive conclusions from the results.

CHAPTER 6: CONCLUSIONS AND FUTURE RECOMMENDATIONS

6.1 Discussion

Typically, most endoscopists follow a standard approach to balloon dilation for benign esophageal strictures. This involves a gradual balloon dilation where the balloon is inflated to each inflation pressure (atm) to achieve a particular balloon diameter until the largest balloon diameter is reached. The initial dilator size chosen approximates the diameter of the stricture for the dilator or may be slightly larger. Each balloon dilator diameter is usually held for 30-60 seconds then inflated to the next largest balloon diameter size of the balloon catheter. When using a mechanical dilator, the "rule of three" is followed to achieve an adequate dilator of the stricture without any complications such as excessive bleeding or perforation. When using a balloon dilator, the stopping point of dilation is quite arbitrary based on the experience of the endoscopist. For instance, the endoscopist may choose to stop as soon as there is a therapeutic mucosal tear or excessive bleeding on endoscopic examination. Others may choose to stop dilation at a certain diameter of the balloon regardless. In the standard approach, a repeat balloon dilation is done when the patient has recurrence of dysphagia. In clinical practice, how balloon dilation is performed is vast based on endoscopist preference rather than data driven. This begs the question that there should be a more standardized and data driven approach to balloon dilation of benign esophageal stricture that if efficient, effective, and safe.

Our progressive approach involves a gradual non-stop inflation of balloon diameter over or more 3 minutes from the smallest to largest balloon diameter size of that balloon catheter. The initial balloon diameter size is 12mm, regardless of the size of the stricture size. The goal is to achieve 16-18mm or more luminal diameter after the dilation session.

By performing a gradual balloon dilation, we can achieve an adequate luminal diameter safely without the dreaded complication of perforation. The procedure is then repeated every 2-3 weeks depending on the final lumen diameter achieved despite if symptomatic relief occurred after the first dilation. By achieving a larger enough lumen diameter of >16-18mm, we believe that patients will have a higher chance of symptomatic relief (dysphagia) and decrease the rate of stricture recurrence.

Despite vast amounts of data on the technicality of how to dilate, unfortunately there is no consensus on a systematic and safe approach to limit complications and result in long term symptomatic improvement. There is also no consensus on how frequent the interval of balloon dilations should be performed. It is well established that balloon or mechanical dilation is an effective and safe approach to benign esophageal stricture. A few preliminary studies have been conducted in recent years that shed light on specific aspects of our progressive approach to balloon dilation for esophageal strictures. The study by Nishikawa et al demonstrated the interacting factors that inflation pressure, dilation force and diameter of the stricture play in the end results of the stricture. By tailoring one or more of these technical aspects, we can develop a more standardized approach that is not only effective and safe but able to achieve long term relief of dysphagia with less need to repeat endoscopic procedures in the future.

6.2 Conclusions

Our retrospective study demonstrated that balloon dilation for benign esophageal stricture with our proposed technique had a considerable symptomatic improvement in their dysphagia and improvement in the lumen size of the stricture. Dilation of least 16 mm or more resulted in a significant prolongation of the dilation-free period. Most studies seem

to stop at 15-16mm lumen diameter but increasing the target diameter of endoscopic dilation up to 18-20mm may be more effective.

Our study sheds light on the possibility that our novel progressive approach improves the patient's dysphagia without causing complications, although further investigation is warranted in the form of a prospective randomized trial. This study will build onto the current medical knowledge and lead to significantly better endoscopic management for benign esophageal strictures. With our cavalier approach to dilating benign esophageal strictures more aggressively but safely we discard the rule of three and do a more standardized technique that is individualized to the type of esophageal stricture and patients' needs.

In conclusion, this study demonstrates the following: 1) endoscopic dilation can achieve luminal remediation with a high degree of technical success and a low complication rate; 2) strictures require frequent dilation at short intervals especially due to etiologies with a high recurrence rate such as anastomotic, radiation or caustic strictures. Although endoscopic esophageal dilation is considered the best initial therapeutic approach for benign esophageal strictures, the best technique to perform the procedure remains to be determined.

6.3 Future Recommendations

Due to the retrospective nature of the study, we can only make assumptions of the results, but future investigation should validate the results of our studies with a double blind prospective randomized design. In this study, we demonstrated that progressive approach to endoscopic dilation of benign esophageal strictures to a target diameter of more than 16mm every 2-3 weeks as needed seemed to result in resolution of the dysphagia without

an increased risk of complications. However, due to the limited data available and patients without long term follow up we cannot determine if the progressive approach was associated with a long-term dilation-free period.

Future research should focus on simple or complex strictures with well-constructed studies comparing various aspects of the progressive approach to balloon dilation modality to identify ideal treatment algorithms. Most of the research studies in the literature either focus on benign esophageal strictures in general or on one etiology, commonly radiation induced or anastomotic stricture. Since peptic induced strictures are the most common cause of benign esophageal strictures encountered by gastroenterologist, I suggest focused study on this etiology using the progressive endoscopic dilation approach. There can also be focused studies on caustic, radiation induced, eosinophilic esophagitis or anastomotic structures, given their recurrent and refractory tendency. Each etiology of benign strictures responds differently and therefore, each such be investigated separately using the progressive endoscopic approach. Although dysphagia caused by peptic esophageal strictures tend to be milder and easier to manage in the short term, recurrent strictures necessitating repeat endoscopic dilatation is a significant problem in the long term due to the chronic nature of gastroesophageal reflux disease (47). Future research should investigate the response of recurrent or refractory strictures with our progressive endoscopic approach.

However, the cost-effectiveness of dilation to >16 mm and the maximum increase in diameter during a single session of endoscopic dilation might be the subject of future research. Besides a potential benefit in cost-effectiveness, more effective treatment of benign esophageal strictures may also affect the quality of life. Every esophageal stricture

has its own characteristics and difficulties therefore, some individualized variation in technique may be needed for successful therapy.

APPENDIX

Table 1.1: Common Etiologies of Benign Esophageal Strictures
Peptic (reflux induced)
Schatzki's ring
Eosinophilic Esophagitis
Radiation induced
Anastomotic (Post-surgical - Esophagus)
Caustic Ingestion
Photodynamic Therapy

Table 2.1: Demographic and Clinical Characteristics of Preliminary Study Patients	
Variable	No. (%)
Age, mean, (range)	64 (27-86)
Male	11 (58%)
Female	8 (42%)
Etiology:	
Peptic	14 (73.6%)
Anastomotic	1 (5.3%)
Eosinophilic Esophagitis	3 (15.8%)
Radiation	1 (2.3%)
Location in esophagus	
Upper	3 (15.8%)
Mid	4 (21.1%)
Distal	11 (57.9%)
Upper and Distal	1 (5%)
Stricture Diameter (mm)	
6mm	1 (5.2%)
>6mm-9mm	10 (53%)
>9-10mm	8 (42%)

Table 3.1: Demographic and Clinical Characteristics of Secondary Study Patients	
Variable	No. (%)
Age, mean, (range)	58 (22-86)
Male	14 (51.9%)
Female	13 (48.1%)
Etiology:	
Peptic	18 (66.7%)
Anastomotic	4 (14.8%)
Eosinophilic Esophagitis	3 (11.1%)
Radiation	1 (3.7%)
Post Heller myotomy	1 (3.7%)
Location in esophagus	
Upper	3 (11.1%)
Mid	4 (14.8%)
Distal	20 (74.1%)
Stricture Diameter (mm)	
6mm	3 (11.1%)
>6mm-9mm	13 (48.1%)
>9-10mm	11 (40.7%)

Table 3.2 : Endoscopic Balloon Dilation Characteristics of Secondary Study	
Variable	No. (%)
Starting Treatment Dilation size (mm)	
<15mm	5 (18.5%)
15mm	11 (40.7%)
>15mm	11 (40.7%)
End Treatment Dilation Size (mm)- Last session	
<15mm	4 (14.8%)
15-<18mm	7 (25.9%)
18mm	9 (33.3%)
Number of Balloon Dilation(s) - End of Therapy	
1 Dilation	10 (37%)
2 Dilations	9 (33%)
3 Dilations	4 (15%)
>3 Dilations	4 (15%)
Clinical Success (Dysphagia Resolved) n=22 with follow up data n= 5 unknown (no follow up data)	
Yes	21 (95%)
No	1 (4.5%)
Procedural Complications	None

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Magna Cum Laude **02/2011-03/2013**
Capstone Project: Meaningful Use Criteria
Honors: Valedictorian

University of Kentucky
Lexington, KY
PhD of Clinical and Translational Science **08/2015-Expected 12/2022**

INTERNSHIP AND RESIDENCY

Texas Tech University Health Sciences Center
El Paso, Texas
General Surgery Resident **07/2011-06/2012**

Texas Tech University Health Sciences Center
El Paso, Texas
Internal Medicine Resident **07/2012-06/2015**

University of Kentucky Medical Center
Lexington, Kentucky
Chief Gastroenterology Fellow **07/2015-06/2018**

Maine Medical Center
Portland, Maine
Advanced Endoscopy Fellow **07/2018-06/2019**

WORK EXPERIENCE

Gastroenterology Associate, P.C.
Casper Wyoming
Gastroenterology/Advanced Endoscopist **08/2019- Present**

Sound Physicians
St. Joseph's Hospital – Bangor, Maine
Hospitalist (Locums Tenens) **07/2018-06/2019**

Pen Bay Medical Center
Rockport, Maine
Hospitalist (Locums Tenens) **07/2018-06/2019**

APOGEE Physicians
Hospital Locations: Morehead and Somerset, Kentucky
Hospitalist (Locums Tenens) **05/2016-06/2018**

EmCare
Hospital: Frankfort Regional Medical Center- Frankfort, Kentucky
Hospitalist (Locums Tenens) **09/2016-06/2018**

Our Lady of Bellefonte Hospital
Ashland, Kentucky
Hospitalist (Locums Tenens) **09/2016-06/2018**

VOLUNTEER EXPERIENCE

Outreach Program
Cebu, Philippines
Volunteer **06/2005-05/2009**

Medical Staff Performance Improvement (MSPI)
El Paso, TX
Volunteer **07/2012-06/2015**

Clinical Operations Committee (COC)
El Paso, TX
Volunteer **07/2013-06/2015**

Patient Safety Council (PSI)
El Paso, TX
Volunteer **07/2013-06/2015**

International Scientific Information: American Journal of Case Reports
New York, NY
Editorial Board Member **09/2013- 06/2015**

Rota Care/Texas Tech Free Clinic
El Paso, TX
Volunteer **09/2014-06/2015**

International Scientific Information: Medical Science Review
New York, NY
Assistant Editor **04/2014- 06/2015**

BioMedical Center – BMC Research Notes: Case Reports Section
London, United Kingdom
Associate Editor **04/2014- 06/2015**

International Scientific Information: Medical Science Case Reports
New York, NY
Assistant Editor **07/2014-6/2015**

LICENSURE

Texas, USA (General Surgery, Physician in Training): 07/2011-06/2012
Texas, USA (Internal Medicine, Physician in Training): 07/2012-6/2015
Kentucky, USA (Internal Medicine/Gastroenterology, License): 06/2015-03/2019
Maine, USA (Internal Medicine/Gastroenterology, License): 09/2017-03/2020
Wyoming, USA (Internal Medicine/Gastroenterology, License): 06/2019-Present

PROFESSIONAL MEMBERSHIPS

2013-Present Member, American College of Gastroenterology (ACG)

2013-Present Member, American Gastroenterology Association (AGA)

2015-Present Member, American Society of Gastrointestinal Endoscopy (ASGE)

AWARDS AND HONORS

2003 Cum Laude, West Virginia State University, Institute, WV

2009 Cum Laude, Cebu Doctors' University College of Medicine, Cebu, Philippines

2013 Servant Leadership Award, Seton Hall University, South Orange, NJ

2013 Magna Cum Laude and Valedictorian, Seton Hall University, South Orange, NJ

2013 PGY-1 Internal Medicine Resident of the Year,
Texas Tech University, El Paso, TX

2014 2nd Annual Outstanding Research Accomplishments Award,
Texas Tech University, El Paso, TX

RESEARCH AND PUBLICATIONS

CASE REPORTS

1. Cooper C, Bilbao JE, Said S, Alkhateeb H, Bizet J, Elfar A, Davalos O, Meza AT, Hernandez GT. "Serum Amyloid A Renal Amyloidosis in a Chronic Subcutaneous ("Skin Popping") Heroin User". Journal of Nephropathology. 2013; 2(3):196-200.

2. Said S, Cooper CJ, Alkhateeb H, Elhanafi S, Bizet J, Gosavi S, Abedin Z. "Pyridostigmine-induced high grade SA-block in a patient with myasthenia gravis." American Journal of Case Reports. 2013;14:359-361.

3. Said S, Cooper CJ, Alkhateeb H, Gosavi S, Alozie O. "Septic Cerebral Vein Thrombosis and Abnormal Leptomeningitis as a Complication From a Periodontitis in a Hispanic Male: Case Report and Literature Review." Journal of Medical Cases. 2013;4(9):598-601.

4. Cooper CJ, Said S, Khalillullah S, Gosavi S, Alozie O. "Unrelenting Lower Back Pain in an Uncontrolled Diabetic Patient With an Uncommon Diagnosis." Journal of Medical Cases. 2013;4(9):602-604.

5. Cooper CJ, Said S, Rosa P, Teleb M, Didia SC. "An Immunocompetent Patient with a Vesicular Rash and Neurological Symptomatology. Case Reports in Medicine. 2013. doi: 10.1155/2013/168943.

6. Said S, Cooper CJ, Reyna E, Alkhateeb H, Diaz J, Nahleh Z. "Paraneoplastic limbic encephalitis, an uncommon presentation of a common cancer: Case report and Discussion." American Journal of Case Reports. 2013;14:391-394.

7. Cooper CJ, Gerges AS, Anekwe E, Hernandez GT. "Double superior vena cava on fistulogram: A case report and discussion." American Journal of Case Reports. 2013;14:395-397.

8. Cooper CJ, Said S, Khalillullah S, Salameh HJ, Hernandez GT. "Multicystic dysplastic kidney complicated by pyelonephritis."American Journal of Case Reports. 2013;14:412-415.

9. Said S, Cooper CJ, Chowdhury F, Nunez A, Quansah R, Davis HE 2nd. "A case with unusual stroke and fulminant outcome in a Hispanic male." American Journal of Case Reports. 2013;14:424-429.

10. Cooper CJ, Said S, Nunez A, Quansah R, Khalillullah S, Hernandez GT. "Dural arteriovenous fistula discovered in patient presenting with recent head trauma." American Journal of Case Reports. 2013;14:444-448.

11. Cooper CJ, Said S, Nunez A, Alkhateeb H, McCallum RW. “Chronic vomiting and diarrhea in a young adult female.” American Journal of Case Reports. 2013;14:449-452.

12. Cooper CJ, Said S, Quansah R, Khalillullah S, Alozie O. Pneumococcal meningitis in a young adult female with common variable immunodeficiency. American Journal of Case Reports. 2013;14:471-475.

13. Alkhateeb H, Said S, Cooper CJ, Gaur S, Porres-Aguilar M. “DRESS syndrome following ciprofloxacin exposure: An unusual association.” American Journal of Case Reports. 2013;14:526-528.

14. Elhanafi S, Othman M, Sunny J, Said S, Cooper CJ, Alkahateeb H, Quansah R, McCallum R. “Esophageal Perforation Post Pneumatic Dilatation for Achalasia Managed by Esophageal Stenting.” American Journal of Case Reports. 2013;14:532-535.

15. Said S, Cooper CJ, Quevedo K, Rodriguez E, Hernandez GT. “Biventricular non-compaction with predominant right ventricular involvement, reduced left ventricular systolic and diastolic function, and pulmonary hypertension in a Hispanic male.” American Journal of Case Reports. 2013; 14:539-542**.**

16. Cooper CJ, Said S, Alkhateeb H, Rodriguez E, Trien R, Ajmal S, Blandon PA, Hernandez GT. “Dilated Cardiomyopathy Secondary to Chronic Cocaine Abuse: A Case Report.” BioMedical Central Research Notes. 2013;16(6):536.

17. Said S, Cooper CJ, Hernandez GT. Resolution of Complete Atrioventricular Block in a Patient with Severe Hypothyroidism. Journal of Case Reports and Studies. 2013;1(3):1-4.

18. Cooper CJ, Said S, Hernandez GT. Recurrent skin, and lung infection in a patient with hyperIgE syndrome. Case Reports in Immunology. 2014.

19. Quansah R, Cooper CJ, Said S, Bizet J, Paez D, Hernandez GT. “Hepatitis C - and HIV induced Porphyria Cutanea Tarda. ” American Journal of Case Reports. 2014;15:35-40.

20. Said S, Cooper CJ, Teleb M, Hernandez GT. Descending necrotizing mediastinitis of odontogenic origin in a young male patient: case report and discussion. American Journal of Medical Case Reports. 2014;15:44-47.

21. Alkhateeb H, Said S, Cooper CJ, Elhanafi S, Teleb M, Saifuddin F, Mukherjee D, Abbas A, Davis HE 2nd. “Myopericarditis as a complication of nonspecific colitis.” American Journal of Case Reports. 2014; 15:82-84.

22. Otoukesh S, Cooper CJ, Lou W, Mojtahedzadeh M, Nasrazadani A, Wampler M, Nahleh Z. Combination chemotherapy regimen in a patient with metastatic malignant

pheochromocytoma and neurofibromatosis type 1. American Journal of Case Reports. 2014;15:123-127.

23. Bizet J, Cooper CJ, Quansah R, Rodriguez E, Teleb M, Hernandez GT. Chorea, Hyperglycemia, Basal Ganglia Syndrome (C-H-BG) in an Uncontrolled Diabetic Patient with Normal Glucose Levels on Presentation. American Journal of Case Reports. 2014;15:143-146.

24. Said S, Cooper CJ, Nwosu A, Bilbao J, Hernandez GT. Hypertension, renal failure, and edema in a 38-year-old man: Light chain deposition disease: A case report and review of the literature. Journal of Nephropathology. 2014;3(2):63-68.

25. Cooper CJ, Teleb M, Elhanafi S, Ajmal S, Hernandez GT. Bird fanciers' lung induced by exposure to duck and goose feathers. American Journal of Case Reports. 2014;15:155-158.

26. Trien R, Cooper CJ, Paez D, Colon E, Ajmal S, Salameh H. Interferon-alpha induced sarcoidosis in a patient being treated for hepatitis C. American Journal of Case Reports. 2014;15:235-238.

27. Cooper CJ, Said S, Popp M, Rodriguez C, Porres-Aguilar M, Alozie O. "A Complicated Case of an Immunocompetent Patient with Disseminated Nocardiosis." Infectious Disease Reports. 2014;6(1):5327.

28. Cooper CJ, Said S. West Nile virus encephalitis induced opsoclonus myoclonus syndrome. Neurology International. 2014;6:12-14.

29. Said S, Alkhateeb H, Cooper CJ, Galvis JM, Fang H, Hernandez GT, Salameh HJ. Primary Central Nervous System Amelanotic Melanoma in a Hispanic male: Case Report. Polish Journal of Radiology. 2014;79:199-202

30. Said S, Cooper CJ, Alkhateeb H, Galvis J, Hernandez GT, Salameh HJ. Moyamoya in Hispanics: not only in Japanese. Neurology International. 2014;6:19-22.

31. Cooper CJ, Otoukesh S, Mojtahedzadeh M, Galvis JM, McCallum RW. Subtotal Gastrectomy as "Last Resort" Consideration in the Management of Refractory Rumination Syndrome. Gastroenterology Research. 2014;7(3-4):98-101.

32. Lauro O, Cooper CJ, Otoukesh S, Mojtahedzadeh M, Didia SC, Torabi A, Nahleh Z. HHV8 (Kaposi Sarcoma) Associated Multicentric Castleman's Disease. Rare Tumors. 2014;6(3):98-100.

33. Said S, Alkhateeb H, Cooper CJ, Rodriguez E, Trien R, Hernandez GT, Salameh H. Idiopathic CD4 Lymphocytopenia in a Non-HIV Hispanic Male. Case Report and Literature Review. International Medical Case Reports Journal. 2014;7:117-120.

34. Alkhateeb H, Said S, Cooper CJ, Cuetter AC. Monomelic amyotrophy involving contralateral upper and lower extremities with an atypical involvement of lower limb muscles in a North American Hispanic female: case report and review of literature. Medical Science Case Report. 2014;1:1-5.

35. Bizet J, Cooper CJ, Zuckerman MJ, Torabi A, Mendoza-Ladd A. Colonic Ulcer Bleeding in the Setting of Isolated Invasive *Aspergillus* Infection in an Immunocompromised Patient. Journal of Medical Case Reports. 2014;8:407.

ORIGINAL RESEARCH PAPERS

1. Said S, Cooper CJ, Alkhateeb H, Gosavi S, Dwivedi A, Onate E, Paez D, Abedin Z. Incident of New Onset Atrial Fibrillation in Patients with Permanent Pacemakers, and the Relation to the Pacing Mode. Medical Science Monitor. 2014;20:268-73.

2. Alkhateeb H, Said S, Cooper CJ, Rodriguez C, Lee S, Onate E, Dwivedi A, Murherjee D. Clinical Profiles and Outcomes of Acute Aortic Dissection in a Predominantly Hispanic Population. Medical Science Monitor. 2014;20:747-751.

3. Said S, Alkhateeb H, Cooper CJ, Rodriguez-Castro C, Dwivedi A, Rodriguez E, Galvis JM, Popp-Switzer MJ, Liu J, Fanj H, Chhana R, Murherjee D. Left Ventricular Mass Changes Associated with Metabolic Syndrome in Hispanics. Experimental and Clinical Cardiology.2014;20(5):3086-3099.

4. Cooper CJ, Said S, Bizet J, Alkhateeb H, Sarosiek I, McCallum RW. Rapid or normal gastric emptying as new supportive criteria for diagnosing Cyclic Vomiting Syndrome in adults. Medical Science Monitor. 2014. 2014;20:1491-1495.

5. Otoukesh S, Mojtahedzadeh M, Cooper CJ, Tolouian R, Said S, Ortega L, Didia SC, Behazin A, Sherzai D, Blandon P. Lessons from the Profile of Kidney Diseases among Afghan Refugees. Medical Science Monitor. 2014;20:1621-1627.

6. Cooper CJ, Morales A, Othman M. Outcomes of the use of Fully Covered Esophageal Self-expandable Stents in the Management of Colorectal Anastomotic Strictures and Leaks. Diagnostic and Therapeutic Endoscopy. 2014. vol. 2014; Article ID 187541. doi:10.1155/2014/187541.

7. Cooper CJ, Teleb M, Dwivedi A, Rangel G, Sanchez LA, Laks S, Akle N, Nahleh Z. Outcome of CT-guided Percutaneous Radiofrequency Ablation versus Partial or Radical Nephrectomy in the Treatment of Renal Cell Carcinoma. Rare Tumors. 2015;7(1):20-25.

8. Ortiz A, Cooper CJ, Alvarez A, Gomez I, Sarosiek I, McCallum RW. Cardiovascular Safety Profile and Clinical Experience of High Dosing Domperidone Therapy for Nausea and Vomiting. The American Journal of the Medical Sciences. 2015;349(5):421-424.

9. Otoukesh S, Mojtahedzadeh M, Figlin R, Rosenfelt FP, Behazin A, Sherzai D, Cooper CJ, Nahleh ZA. Literature Review and Profile of Cancer Diseases among Afghan Refugees in Iran: Referrals in Six Years of Displacement. Medical Science Monitor. 2015;21:3622-3628.

10. Fleming R, Cooper CJ, Ramirez R, Huerta A, Boman D, Zuckerman MJ. The Varied Clinical and Endoscopic Manifestations of Amebic Colitis. BMC Research Notes. 2015;8(1):781. doi: 10.1186/s13104-015-1787-3.

11.. Majewski M, Sarosiek I, Cooper CJ, Wallner G, Roeser K, Edlavitch, McCallum RW, Sarosiek J. Gastric pH, and Therapeutic Responses to Esomeprazole in Patients with Functional Dyspepsia: Potential Clinical Implications. The American Journal of the Medical Sciences. 2016;352(6):582-592.

REVIEW ARTICLES

1. Said S, Cooper CJ, Didia SC. PCSK9-Inhibitors: A Review of a Novel Approach in Hypercholesteremia Management. Medical Science Review. 2014;1:1-6.

2. Cooper CJ, Said S. Peroral Endoscopic Myotomy (POEM) for Achalasia: A Comprehensive Review. Medical Science Review. 2014;1:7-14.

3. Cooper CJ, McCallum RW. Gastrointestinal Motility and Functional Bowel Disorders, Series #5: Cyclic vomiting syndrome: diagnostic criteria and insights into long term treatment outcomes. Practical Gastroenterology. 2015;39(1):30,32,35-37,47-48.

4. Cooper CJ, Fleming R, Boman D, Zuckerman MJ. The Varied Clinical Manifestations of Amebic Colitis. Southern Medical Journal. 2015;108(11):676-681.

BOOK CHAPTER

1. Cooper CJ, Sunny JK, McCallum RW. Handbook of Gastrointestinal Motility and Functional Disorders. Ch. 12 Rumination Syndrome. 2015;145-155.