Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

ASGE guideline on the management of achalasia

Mouen A. Khashab, MD,[1,*] Marcelo F. Vela, MD,[2,*] Nirav Thosani, MD,[3,*] Deepak Agrawal, MD, MPH, MBA,[4] James L. Buxbaum, MS, FASGE,[5] Syed M. Abbas Fehmi, MD, MSc, FASGE,[6] Douglas S. Fishman, MD, FAAP, FASGE,[7] Suryakanth R. Gurudu, MD, FASGE,[2] Laith H. Jamil, MD, FASGE,[8] Terry L. Jue, MD, FASGE,[9] Bijun Sai Kannadath, MBBS, MS,[3] Joanna K. Law, MD,[10] Jeffrey K. Lee, MD, MAS,[11] Mariam Naveed, MD,[12] Bashar J. Qumseya, MD, MPH,[13] Mandeep S. Sawhney, MD, MS, FASGE,[14] Julie Yang, MD, FASGE,[15] Sachin Wani, MD, ASGE Standards of Practice Committee Chair[16]

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Achalasia is a primary esophageal motor disorder of unknown etiology characterized by degeneration of the myenteric plexus, which results in impaired relaxation of the esophagogastric junction (EGJ), along with the loss of organized peristalsis in the esophageal body. The criterion standard for diagnosing achalasia is high-resolution esophageal manometry showing incomplete relaxation of the EGJ coupled with the absence of organized peristalsis. Three achalasia subtypes have been defined based on high-resolution manometry findings in the esophageal body. Treatment of patients with achalasia has evolved in recent years with the introduction of peroral endoscopic myotomy. Other treatment options include botulinum toxin injection, pneumatic dilation, and Heller myotomy. This American Society for Gastrointestinal Endoscopy Standards of Practice Guideline provides evidence-based recommendations for the treatment of achalasia, based on an updated assessment of the individual and comparative effectiveness, adverse effects, and cost of the 4 aforementioned achalasia therapies. (Gastrointest Endosc 2020;91:213-27.)

INTRODUCTION

Achalasia is a primary esophageal motor disorder of unknown etiology characterized by degeneration of the myenteric plexus, which results in impaired relaxation of the esophagogastric junction (EGJ), along with the loss of organized peristalsis in the esophageal body. These abnormalities typically lead to dysphagia and regurgitation.[1] Achalasia occurs equally in males and females. Achalasia has traditionally been viewed as a rare disease, with a globally reported incidence varying from .03 to 1.63 per 100,000 persons per year.[2] However, most estimates of incidence have been derived from retrospective searches of hospital discharge databases, with the diagnosis based on older diagnostic techniques such as conventional manometry or barium esophagram. More recent studies incorporating state-of-the-art high-resolution manometry and data derived from motility laboratory databases suggest a higher incidence of 2.92 of 100,000 in Central Chicago[2] and 2.3 to 2.8 of 100,000 in South Australia.[3]

DIAGNOSIS OF ACHALASIA

Esophageal motor abnormalities in achalasia lead to symptoms of dysphagia for solids and liquids without oropharyngeal transfer difficulties in roughly 90% of patients, regurgitation in 75%, weight loss in 60%, chest pain in 50%, and heartburn in 40%.[4] In patients with a clinical presentation suggestive of achalasia, endoscopy is mandatory to exclude pseudoachalasia or other forms of mechanical obstruction at the EGJ.[1] Although endoscopy may often reveal esophageal dilation, retention of food and secretions, and a "puckered" EGJ, these findings are not diagnostic of achalasia and endoscopy may be normal, especially in early stages of the disease before esophageal dilation ensues. Barium esophagram can be very helpful, particularly when the typical "bird beak" appearance at the EGJ with upstream esophageal dilation is found, but as with endoscopy, an esophagram may be unrevealing when the esophagus is not dilated. A modified esophagram with timed emptying of a standardized barium volume, known as the "timed

barium esophagram," is preferable because in addition to aiding diagnosis, it has been shown to be useful as a means to objectively document treatment outcomes and predict symptom recurrence.[5]

The criterion standard for diagnosing achalasia is high-resolution esophageal manometry showing incomplete relaxation of the EGJ coupled with the absence of organized peristalsis. Three achalasia subtypes have been defined based on the high-resolution manometry findings in the esophageal body: type I or classic achalasia with low intraesophageal pressure, type II with pan-esophageal pressurization, and type III with high-amplitude spastic contractions.[6] Importantly, multiple studies have shown that treatment outcomes are dependent on achalasia subtype, and this information can guide the choice of therapy.[7-9] Based on available data, pneumatic dilation, laparoscopic Heller myotomy, and peroral endoscopic myotomy (POEM) are all believed to be efficacious for achalasia types I and II, whereas POEM has emerged as the preferred treatment for achalasia type III.[10]

The endoluminal functional lumen imaging probe (EndoFLIP, Crospon, Galway, Ireland) is a new technology that enables assessment of the mechanical properties of the esophagus and EGJ, using impedance planimetry measurements of luminal cross-sectional area, along with pressure changes during volume-controlled distension.[11] Studies using EndoFLIP have shown that EGJ distensibility is reduced in achalasia patients,[12] and symptomatic failure after treatment is associated with persistently low distensibility.[13] Furthermore, a recent small study showed that achalasia could be diagnosed by EndoFLIP in a subset of achalasia patients in whom high-resolution manometry revealed normal EGJ relaxation.[14] Although this technique is new and our understanding of its role in achalasia is evolving, it appears that EndoFLIP provides additional and complementary information in the evaluation and management of achalasia patients.

AIM AND SCOPE

In the last decade, there have been considerable advances in the evaluation and management of achalasia. From a diagnostic perspective, high-resolution manometry has become the criterion standard, leading to the definition of 3 achalasia subtypes that have confirmed implications for response to and choice of therapeutic modality. Furthermore, EndoFLIP is emerging as a useful technique for diagnosis and objective assessment after therapy. Although botulinum toxin injection, pneumatic dilation, and laparoscopic Heller myotomy have been available for many years, the treatment of achalasia has been revolutionized with the advent of POEM, which has become a routine procedure in many centers around the world. A wealth of data examining the effectiveness of POEM has become available over the last few years, including several meta-analyses. The aim of this document is to provide evidence-based recommendations for the treatment of achalasia, based on an updated assessment of the comparative effectiveness, adverse effects, and cost of achalasia therapies.

METHODS

Overview

This document was prepared by a working group of the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE). It includes a systematic review of available literature along with guidelines for the role of endoscopy in management of achalasia using criteria highlighted in Table 1.[15] After evidence synthesis, recommendations were drafted by the full panel during a face-to-face meeting on March 16, 2018, and approved by the Standards of Practice committee members and the ASGE Governing Board.

Panel composition and conflict of interest management

The panel consisted of 2 content experts (M.A.K., M.F.V.), a committee member with expertise in systematic reviews and meta-analysis (N.T.), the committee chair (S.W.), and other committee members. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies (see ASGE Conflict of Interest and Resolution Policy at https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf?sfvrsn=2; the committee member Conflict of Interest disclosure in the Conflict of Interest Principles for ASGE Publication and Educational Product Development Excluding Gastrointestinal Endoscopy and CME Activity at https://www.asge.org/docs/default-source/about-asge/mission-and-governance/doc-asge-publications-coipolicy_2009.pdf?sfvrsn=6).

Formulation of clinical questions

For all clinical questions, potentially relevant patient-important outcomes were identified a priori and rated from "not important" to "critical" through a consensus process. Relevant clinical outcomes included (1) clinical success as defined by Eckardt score ≤ 3; (2) rate and severity of adverse events; (3) length of hospital stay; (4) recurrence rate during long-term follow-up; and (5) rate of GERD with pH studies, rate of erosive esophagitis, and proton pump inhibitor use.

Literature search and study selection criteria

Separate literature searches were conducted for botulinum toxin injection, pneumatic dilation, and myotomy (laparoscopic Heller myotomy and POEM) in the treatment of achalasia. A medical librarian performed a comprehensive literature search from inception to October 17, 2017,

TABLE 1. System for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	We are very confident that the true effect lies close to that of the estimate of effect.	⊕⊕⊕⊕
Moderate quality	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.	⊕⊕⊕◯
Low quality	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.	⊕⊕◯◯
Very low quality	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	⊕◯◯◯

Adapted from Guyatt et al.[15]

in the following databases: Ovid Medline(R) epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R); Embase (Elsevier); and Wiley Cochrane Library. The searches were limited to English language articles with animal studies excluded. No date limits were applied. Combinations of subject headings and text words were used, including Esophageal Achalasia OR cardiospasm OR achalasia OR megaesophagus OR mega-esophagus OR megaoesophagus OR mega-oesophagus AND Botulinum Toxins OR botulin* OR botox OR myotomy OR Heller OR peroral OR per oral OR POEM OR LHM OR Dilatation/ OR dilatation. Detailed search strategies can be viewed in Appendix 1 (available online at www.giejournal.org).

For each of the treatment modalities, a literature search for existing systematic reviews and meta-analyses was performed. If none was identified, a full systematic review and meta-analysis (when possible) was conducted using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria.[16] Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa), and duplicates were removed. The EndNote library was then uploaded into Covidence (www.covidence.org). Studies were first screened by title and abstract and then by full text, and all conflicts were resolved by consensus. If existing systematic reviews and meta-analyses were available, inclusion and exclusion criteria were reviewed, and methodologic quality of the study was assessed using the measurement tool to assess systematic reviews (Assessing the Methodological Quality of Systematic Reviews-2 [AMSTAR-2], https://amstar.ca/Amstar_Checklist.php). Only systematic reviews and meta-analyses meeting the quality thresholds were used for data synthesis. When applicable, available systematic reviews and meta-analyses were updated based on literature review as described above.

Data extraction and statistical analysis

If data extraction was needed for a meta-analysis, data were extracted by 2 independent reviewers using Microsoft Excel (Microsoft Corporation, Redmond, Wash). The primary estimate of effect was based on a priori identified outcomes of interest. For outcomes with limited or no available direct comparisons, indirect comparisons were used to estimate the magnitude and direction of effect. Heterogeneity was assessed using the I^2 and Q statistic. Significant heterogeneity was defined at $I^2 > 50\%$ and significant P value (<.05) on the Q statistic. Random-effects models were used if significant heterogeneity was detected. Otherwise, fixed-effects models were used. Studies were weighted based on their size. A priori sources of heterogeneity for each outcome were hypothesized and addressed in sensitivity analyses when applicable. Publication bias was assessed using funnel plots and the classic fail-safe. Statistical analyses were performed using Comprehensive Meta Analysis V_3 (Biostat Inc, Englewood, NJ).

Certainty in evidence (quality of evidence)

The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding.

Considerations in the development of recommendations

During an in-person meeting, the panel developed recommendations based on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, the assumptions about the values and preferences associated with the decision along with available data on resource utilization, and cost-effectiveness. The final wording of the recommendations (including direction and strength), remarks, and qualifications were decided by consensus using criteria highlighted in Table 1,[15] and were approved by all members of the panel. The strength of individual recommendation is based on the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "we

suggest…," whereas stronger recommendations are typically stated as "we recommend…."

RESULTS

Treatment of achalasia

Although up to 5% of achalasia patients may require esophagectomy for end-stage achalasia,[4] this document focuses on the treatment modalities currently used for managing most patients with achalasia: botulinum toxin injection, pneumatic dilation, laparoscopic Heller myotomy, and POEM. It is important to note that when assessing the literature that describes the effectiveness of achalasia treatments, widely varying definitions of therapeutic success are encountered across different studies. For instance, symptomatic success may be defined very strictly in some studies and more liberally in others, and not all studies use a standardized score to determine treatment success. Furthermore, not all studies provide objective measures of treatment success such as changes in lower esophageal sphincter (LES) pressure or timed barium emptying, and when these are provided, the definition of success may also vary. Finally, a very important outcome from the perspective of adverse effects of achalasia therapies is the development of GERD, the definition of which differs across studies, and may include symptoms, esophagitis on endoscopy, or pH monitoring. Therefore, wherever possible, we have restricted our review and analysis of treatment outcomes to studies that documented the Eckardt score as a measure of therapeutic success.[17] The Eckardt score is based on the summation of 4 symptoms (dysphagia, regurgitation, chest pain, weight loss) that are graded according to severity, and treatment success is defined as a score $\leq$3.[17] Although the Eckardt score may have some shortcomings that are outside the scope of this document,[18] it is the most widely used metric for assessing clinic outcomes in achalasia and provides a standardized measure of treatment success.

Botulinum toxin injection. Endoscopy-based injection of botulinum toxin reduces LES pressure by inhibiting release of acetylcholine from nerve endings.[19] It is considered to be generally very safe, and serious adverse events such as mediastinitis or allergic reactions are exceedingly rare.[1] The main shortcoming of this treatment approach is its durability, which is limited to months.

We conducted a systematic review and meta-analysis of 22 uncontrolled studies that reported the clinical outcome in 730 achalasia patients who were treated with botulinum toxin injection.[20-41] Clinical success, defined by an Eckardt score $\leq$3, was achieved in 77% (95% confidence interval [CI], 72%-81%; I^2 value = 35; P = .04) over a follow-up period ranging from 1 to 6 months (Fig. 1). There was a statistically significant decrease in average LES pressure from 38.23 mm Hg (range, 34.40-42.06) before the procedure to 23.30 mm Hg (range, 20.79-25.81) after botulinum toxin injection (P < .01). Serious adverse events were not described, GERD after treatment was not documented, and chest pain was reported by 11% (95% CI, 7%-15%) of patients. Similarly, in a recent multicenter review of adverse events after botulinum toxin injection for esophageal motor disorders involving 661 injections in 386 patients, transient chest pain was the most common adverse event, reported after 4.4% of injections.[42]

Pneumatic dilation. Pneumatic dilation disrupts the LES fibers through intraluminal dilation of a pressurized balloon and is most commonly performed under fluoroscopic guidance. Three balloon sizes (30, 35, and 40 mm diameter) are available for pneumatic dilation. The conventional approach is to start with the 30-mm balloon in most patients, progressing to bigger diameter balloons if a response is not achieved.

A literature search did not identify a systematic review or meta-analysis evaluating pneumatic dilation as a treatment for achalasia in uncontrolled trials. We therefore conducted a systematic review and meta-analysis of 52 uncontrolled studies that reported outcomes in 4166 achalasia patients treated with pneumatic dilation.[17,43-93] Clinical success, defined by an Eckardt score $\leq$3, was achieved in 83% (95% CI, 79%-85%; I^2 value = 82.23; P < .01) over a follow-up period ranging from 3 to 6 months (Fig. 2). There was a statistically significant decrease in average LES pressure from 34.47 mm Hg (range, 32.82-36.13) before the procedure to 20.80 mm Hg (range, 12.11-29.49) after pneumatic dilation (P < .01).

Of note, when assessing outcomes of pneumatic dilation, it is important to keep in mind that the conventional clinical approach involves a "graded dilation" strategy that allows progression to larger balloons if needed. However, in some trials, treatment success focused on the response to a single dilation, and progression to a larger balloon was deemed a treatment failure. The response to graded pneumatic dilation is the most relevant outcome for clinical practice. Most included studies did not clarify whether the reported clinical success was achieved after a single dilation or with graded dilations. Common perioperative adverse events reported in the studies included esophageal perforation (2.8%; 95% CI, 2.3%-3.5%) and substantial bleeding requiring interventions (2%; 95% CI, 1%-4%). After an average follow-up period of 6 months, rate of symptomatic GERD was 9% (95% CI, 5%-16%).

Laparoscopic Heller myotomy. The technique for surgical myotomy to disrupt the LES fibers through an incision has evolved from open surgery (thoracoscopy and laparotomy) to the current standard, which is a minimally invasive laparoscopic myotomy with a partial fundoplication. The outcomes of laparoscopic Heller myotomy were described in a recent meta-analysis that included 5834 patients in 53 studies (5 randomized controlled trials and 48 prospective or retrospective cohort studies).[94] In this meta-analysis, clinical success was not based strictly on the Eckardt score. Instead, the main outcome measure was improvement of dysphagia, which was treated as a

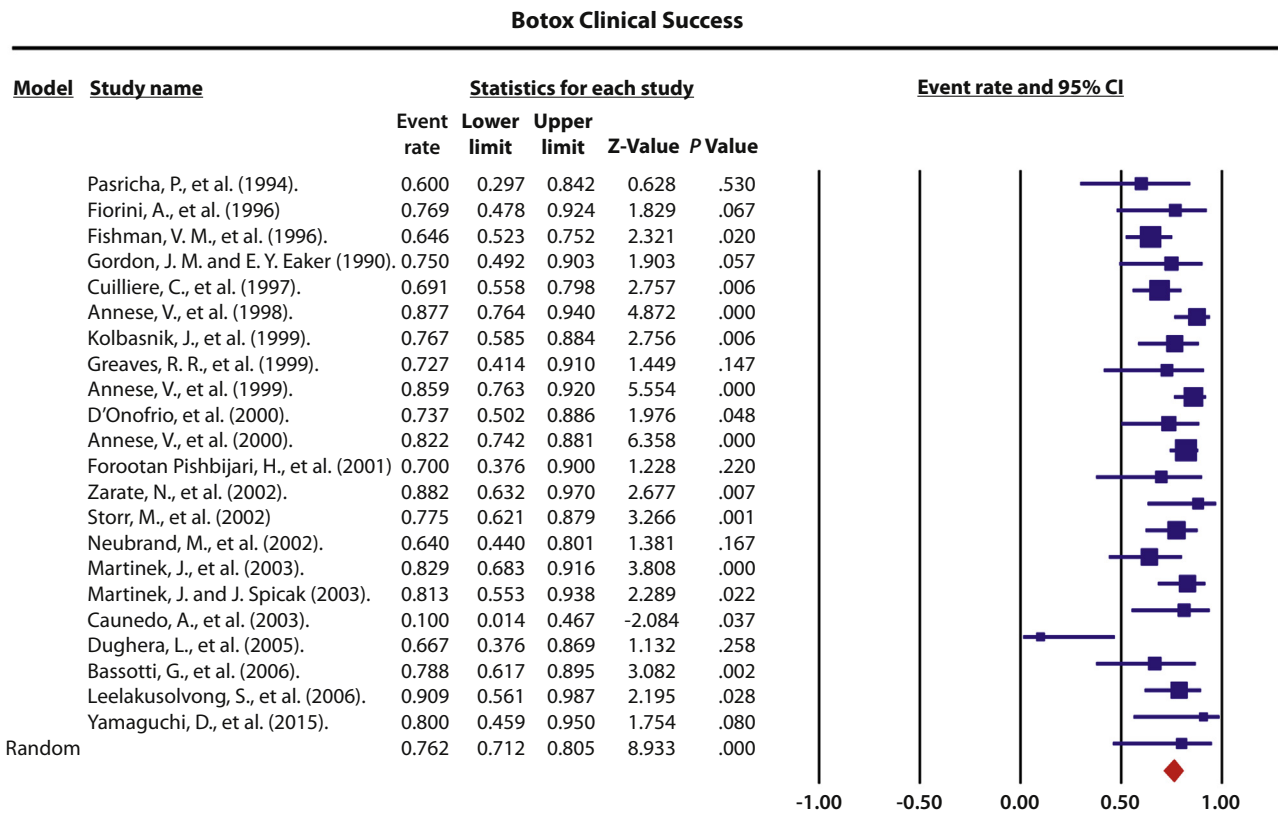

Figure 1. Forrest plot of trials assessing clinical success for botulinum toxin injection. *CI*, Confidence interval.

dichotomous variable. Averaged across all studies, dysphagia improvement was reported by 87.7% (95% CI, 87%-88%) of patients after laparoscopic Heller myotomy, with a mean follow-up of 40 months. Based on linear regression models, the predicted probability for improvement of dysphagia was 91.0% at 12 months and 90.0% at 24 months. Objective measures of treatment success such as findings of manometry and esophagram were not included in this meta-analysis. GERD symptoms were reported by 17.5% (95% CI, 16%-19%) of patients after laparoscopic Heller myotomy, with evidence of GERD by endoscopy in 11.5% (95% CI, 9%-15%) and by pH monitoring in 11.1% (95% CI, 10%-13%). Recurrent or persistent symptoms after laparoscopic Heller myotomy occurred in about 5% to 15% of patients.[95,96]

Peroral endoscopic myotomy. Inoue et al[97] published the first study on POEM in 2010 and reported clinical success in all 17 included patients with associated significant decrease in LES pressure.[97] Since then, multiple retrospective and prospective studies assessing short-, mid-, and long-term efficacy and safety of POEM have been published.[98-112] Akintoye et al[113] performed a meta-analysis that reported on clinical outcomes of POEM. Thirty-six studies involving 2373 patients (52% women, mean age 45 years) were included in this review. The indication for POEM was achalasia in 98% of patients. The mean myotomy length was 12 ± .48 cm, and mean procedure time was 88 ± 5.4 minutes. Clinical success (Eckardt score ≤3) was achieved in 98% (95% CI, 97%-100%) of patients after the procedure. There was, however, significant heterogeneity (I^2 = 68%, P < .001) in the overall results. The mean Eckardt score decreased from 6.9 ± .15 preoperatively to .77 ± .10, 1.0 ± .10, and 1.0 ± .08 within 1, 6, and 12 months of treatment, respectively. In addition, there was a significant decrease in the average LES pressure, integrated relaxation pressure, and the average heights of the barium column after a timed barium esophagram after the procedure. Specifically, the average LES pressure and integrated relaxation pressure decreased from 33 ± 1.7 and 30 ± 1.4 mm Hg before the procedure to 14 ± 1.2 and 13 ± 1.6 mm Hg, respectively, within 6 months of the procedure (P < .05).

Common perioperative adverse events reported in the studies included mucosal injury (4.8%; 95% CI, 2.0%-8.5%), esophageal perforation (.2%; 95% CI, 0%-1.1%),

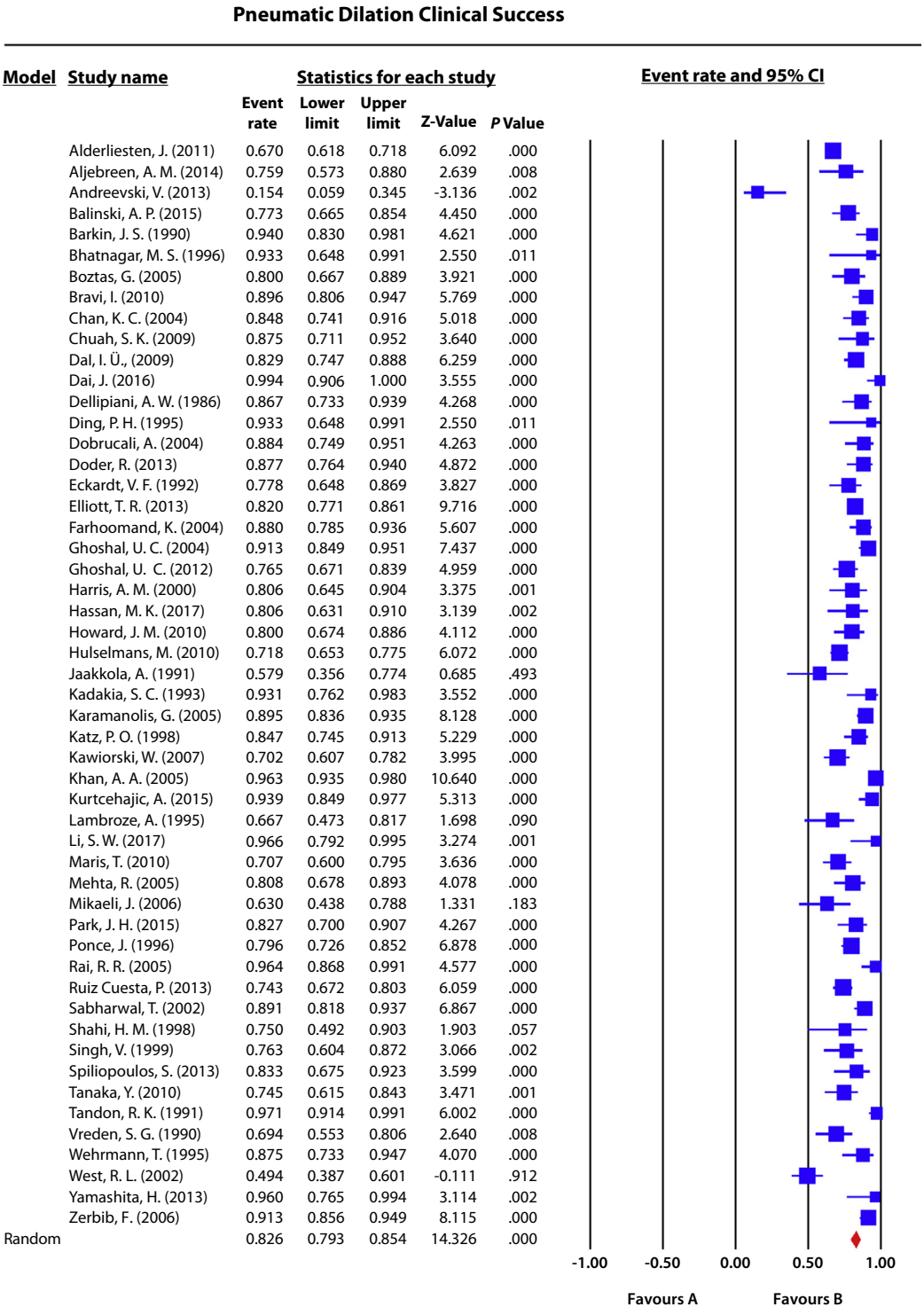

Figure 2. Forrest plot of trials assessing clinical success for pneumatic dilation. *CI*, Confidence interval.

substantial bleeding requiring interventions (.2%; 95% CI, 0%-1.4%), subcutaneous emphysema (7.5%; 95% CI, 3.5%-12%), pneumothorax (1.2%; 95% CI, .1%-4.3%), pneumomediastinum (1.1%; 95% CI, .1%-4.7%), pneumoperitoneum (6.8%; 95% CI, 1.9%-14%), and pleural effusion (1.2%; 95% CI, 0%-8.3%). However, serious adverse events

related to the POEM procedure are rare, and most intraprocedural adverse events (eg, bleeding, mucosotomy, symptomatic pneumoperitoneum) can be addressed and treated endoscopically without any sequelae. One large study that included 1826 patients specifically assessed adverse events related to POEM.[114] A total of 156 adverse events occurred in 137 patients (7.5%). Fifty-one (2.8%) inadvertent mucosotomies occurred, and mild, moderate, and severe adverse events (graded using the ASGE lexicon for grading severity of adverse events) were noted in 116 (6.4%), 31 (1.7%), and 9 (.5%) patients, respectively.[115] Multivariable analysis demonstrated that sigmoid-type esophagus (odds ratio [OR], 2.28; $P = .05$), endoscopist experience <20 cases (OR, 1.98; $P = .04$), use of a triangular tip knife (OR, 3.22; $P = .05$), and use of an electrosurgical current different from spray coagulation (OR, 3.09; $P = .02$) were significantly associated with the occurrence of adverse events. The above study did not assess the long-term adverse events (mainly GERD) of POEM. In the meta-analysis by Akintoye and colleagues,[113] after a mean follow-up of 8 months postprocedure, the rates of symptomatic gastroesophageal reflux, esophagitis on upper endoscopy, and abnormal esophageal acid exposure were 8.5% (95% CI, 4.9%-13%), 13% (95% CI, 5.0%-23%), and 47% (95% CI, 21%-74%), respectively.

Most studies included in the meta-analysis by Akintoye et al[113] reported on short- and mid-term outcomes of POEM. Limited data address long-term outcomes with POEM. Teitelbaum et al[107] recently studied outcomes of POEM at least 5 years after the procedure. Twenty-three achalasia patients with a median follow-up duration of 65 months were included. Eckardt scores were significantly improved from preoperative baseline (1.7 vs 6.4, $P < .001$). Long-term clinical success (Eckardt score ≤ 3) was achieved in 19 patients (83%), and none required retreatment for persistent or recurrent symptoms. Eckardt scores improved at 6 months and were maintained at 2 years; however, there was a small but significant worsening of symptoms between 2 and 5 years. At the 6-month follow-up, repeat manometry showed decreased EGJ relaxation pressures (preoperative, 23 $\pm$ 15 mm Hg, vs postoperative, 9 $\pm$ 7 mm Hg; $P < .01$), and esophagram demonstrated improved emptying. However, pH monitoring showed abnormal distal esophageal acid exposure in 38% of patients.

Management of treatment failures. Although the efficacy of pneumatic dilation, Heller myotomy, and POEM is excellent at a follow-up of 1 to 2 years, as outlined in the previous sections, the effectiveness of these therapies decreases over time. Data regarding long-term outcomes of these treatments are limited, but available studies suggest that retreatment is needed in 23% to 35% of patients 5 to 7 years after pneumatic dilation[116] and in 18% to 27% of patients at a median of 5.3 years after Heller myotomy.[116,117] Retreatment data after long-term follow-up in POEM patients are not yet available, but symptomatic success persisted in 83% of 23 patients followed for at least 5 years.[107]

There is no consensus and no large studies to inform the best course of action in patients who have failed initial treatment or have recurred after prolonged follow-up. Not surprisingly, the response rate is generally lower in these patients, who represent a more difficult group to treat. Few studies have assessed the effect of prior pneumatic dilation and/or botulinum toxin injection on outcomes of POEM. Although prior therapy may result in submucosal fibrosis and prolongation of procedure time,[118] the long-term outcomes are not affected by the aforementioned therapies.[118,119] Several studies have reported on outcomes of POEM after either failed laparoscopic Heller myotomy or failed prior POEM. Recurrent or persistent symptoms after laparoscopic Heller myotomy may occur in up to 21% of patients.[95,96,117,120] Traditionally, these patients are treated with either pneumatic dilation or repeat laparoscopic Heller myotomy. Pneumatic dilation can be performed safely, with a response rate of 50% to 75%.[120,121]

Several studies have reported on the role of POEM in the treatment of patients who failed laparoscopic Heller myotomy. Clinical success rates of 92% to 100% have been reported in this group of patients treated with POEM.[112,121-124] The largest study that compared outcomes of POEM in patients with prior laparoscopic Heller myotomy (n = 90) with patients without prior laparoscopic Heller myotomy (n = 90) showed no difference in the rates of technical success (98% vs 100%, $P = .49$) and adverse events (8% vs 13%, $P = .23$).[112] However, the clinical success rate was lower in the laparoscopic Heller myotomy group (81% vs 94%, $P = .01$).[112]

POEM carries several advantages over redo laparoscopic Heller myotomy in patients who had failed prior laparoscopic Heller myotomy. Clinical success rate of POEM after failed laparoscopic Heller myotomy may be superior to that of repeat laparoscopic Heller myotomy (73%-89%), although there are no currently available head-to-head comparative studies.[95] Furthermore, redo laparoscopic Heller myotomy can be challenging because of the presence of adhesions from the previous surgery, which results in a relatively high perforation rate of 1.5% to 20%.[125] Repeat POEM can also be performed in patients who failed a prior POEM procedure. Two small studies with a total number of 21 patients who underwent redo POEM reported 100% clinical success after a mean follow-up of 11 months.[121,126] A more recent retrospective multicenter study reported on 46 redo POEM procedures with a clinical success rate of 85% at 3 months and an adverse event rate of 17%.[127]

Comparative data between various achalasia treatments

Multiple controlled trials have compared different treatment modalities for achalasia. Based on these trials and corresponding meta-analyses, the comparative effectiveness of botulinum toxin injection, pneumatic dilation,

laparoscopic Heller myotomy, and POEM are summarized below.

Pneumatic dilation versus botulinum toxin injection. Multiple randomized trials have compared the outcomes of pneumatic dilation and intrasphincteric botulinum toxin injection in the treatment of achalasia.[128-135] Leyden et al[136] conducted a systematic review and meta-analysis comparing the efficacy and safety of these 2 endoscopic treatment modalities. Based on the AMSTAR-2 critical appraisal tool, the overall confidence in the result of this meta-analysis was deemed to be "high." Seven randomized clinical trials involving 178 patients were included and 2 studies were excluded on the basis of clinical heterogeneity of the initial endoscopic protocols. There was no significant difference between pneumatic dilation and botulinum toxin arms in clinical success rates within 4 weeks of the initial intervention (risk ratio of remission, 1.11; 95% CI, .97-1.27). There was also no significant difference in the mean esophageal pressures between the 2 groups, with a weighted mean difference for pneumatic dilation of –.77 (95% CI, –2.44 to .91; $P = 0.37$). Clinical success rates beyond 4 weeks were available for 3 studies at 6 months and 4 studies at 12 months. At 6 months, clinical success was achieved in 80.7% of patients (46/57) who underwent pneumatic dilation as compared with 51.8% of patients (29/56) who underwent botulinum toxin injection (risk ratio, 1.57; 95% CI, 1.19-2.08; $P = .0015$). At 12 months, clinical success rates were 73.3% (55/75) and 37.5% (27/72), respectively (risk ratio, 1.88; 95% CI, 1.35-2.61; $P = .0002$). There were no adverse events in the botulinum injection arm (total of 151 injection procedures), whereas perforation occurred in 3 cases (total of 188 pneumatic dilation procedures) in the pneumatic dilation arm. These data demonstrate that pneumatic dilation is a more effective long-term (>6 months) endoscopic treatment option compared with botulinum toxin injection for patients with achalasia.

Pneumatic dilation versus laparoscopic Heller myotomy. We identified 3 recent meta-analyses that compared the clinical efficacy and effectiveness between pneumatic dilation and laparoscopic Heller myotomy.[137-139] Based on the AMSTAR-2 critical appraisal tool, overall quality of meta-analyses performed by Cheng et al[137] was rated "high" and Illes et al[138] and Baniya et al[139] were "moderate." Based on this assessment, we used the results of the meta-analysis conducted by Cheng et al for this document.

Cheng et al[137] conducted a meta-analysis of 7 randomized studies that compared outcomes of pneumatic dilation with laparoscopic Heller myotomy in patients with achalasia. Four of these studies represented 2 trials, with short-term outcomes reported initially followed by reporting of long-term data.[140-143] Therefore, 5 studies involving 498 participants were included in the final analysis. The cumulative clinical success rate was significantly higher with laparoscopic Heller myotomy at 3 months and 1 year (short-term), with risk ratios of 1.16 (95% CI, 1.01-1.35; $P = .04$) and 1.14 (95% CI, 1.02-1.27; $P = .02$), respectively. However, clinical success rates were not different between both groups at both 2-year and 5-year follow-up (long-term), with risk ratios of 1.05 (95% CI, .91-1.22; $P = .49$) and 1.17 (95% CI, .84-1.64; $P = .34$), respectively. Rates of major inadvertent mucosal tears requiring subsequent intervention with laparoscopic Heller myotomy were significantly lower than those of esophageal perforation during pneumatic dilation requiring postprocedural medical, endoscopic, or surgical therapy, with a risk ratio of .25 (95% CI, .08-0.81; $P = .02$).

Last, rates of gastroesophageal reflux (mean difference, .55; 95% CI, .15-2.06; $P = .38$), LES pressures (mean difference, –2.99; 95% CI, –6.03 to .66; $P = .05$), and quality of life scores did not differ in trials with sufficient data. Given the comparable clinical success rates at mid- and long-term follow-up, these data suggest that both treatment options can be proposed as the initial treatment for achalasia.

POEM versus laparoscopic Heller myotomy. There are no published randomized trials comparing outcomes of POEM and laparoscopic Heller myotomy, although data from recently completed trials are eagerly awaited. Multiple retrospective trials have been published comparing outcomes of POEM and laparoscopic Hellter myotomy.[94,144] The meta-analysis by Awaiz et al[144] was rated "high," whereas the meta-analysis by Schlottmann et al[94] was rated "low" as per the AMSTAR-2 critical appraisal tool.

Awaiz and colleagues carried a systematic review and meta-analysis to compare the safety and efficacy of these 2 treatment strategies.[144] Seven trials including a total of 483 patients (laparoscopic Heller myotomy, 250; POEM, 233) were analyzed.[98,100,102,108,145-147] Both arms were comparable in terms of relevant preoperative variables, such as prior endoscopic therapy and prior Heller myotomy. Procedure time was longer for laparoscopic Heller myotomy, but the difference was not statistically significant (weighted mean difference, 26.28 minutes; 95% CI, 11.20-63.70; $P = .17$). The rate of adverse events (OR, 1.25; 95% CI, .56-2.77; $P = .59$), rate of gastroesophageal reflux (OR, 1.27; 95% CI, .70-2.30; $P = .44$), length of hospital stay (weighted mean difference, .30; 95% CI, .24-.85; $P = .28$), postoperative pain score (weighted mean difference, .26; 95% CI, 1.58-1.06; $P = .70$), and long-term gastroesophageal reflux (weighted mean difference, 1.06; 95% CI, .27-4.1; $P = .08$) were similar for both procedures. Based on available data from 3 studies, the rate of short-term clinical treatment failure was significantly higher in patients who underwent laparoscopic Heller myotomy (13% vs .85%; OR, 9.82; 95% CI, 2.06-46.80; $P < .01$). Thus, available data suggest that laparoscopic Heller myotomy and POEM are both acceptable first-line therapies in the management of achalasia patients.

POEM versus pneumatic dilation. There are no published meta-analyses evaluating the comparative effectiveness of POEM versus pneumatic dilation. Our literature search identified only 5 studies directly comparing these

treatment modalities. After excluding 1 study that involved only pediatric patients[148] and another study that limited follow-up to only 2 months,[149] we performed a meta-analysis based on 3 studies that reported the Eckardt score after treatment: 2 retrospective cohort studies[150,151] and a randomized controlled trial.[152] The 3 studies involved 114 patients treated with POEM and 92 patients who underwent pneumatic dilation.

Clinical success (Eckardt score ≤3) 12 months after treatment was achieved in 93% of patients (95% CI, 87%-97%; I^2 value = 0; P = 0.67) treated with POEM and 72% of patients (95% CI, 64%-80%; I^2 value = 54; P = 0.11) after pneumatic dilation, favoring POEM with a risk ratio of 1.28 (95% CI, 1.14-1.45; P < .01) (Fig. 3). There was a trend toward more symptomatic GERD after POEM compared with pneumatic dilation (23% vs 9%). For the 2 studies that reported GERD based on endoscopic findings, erosive esophagitis was more frequent after POEM compared with pneumatic dilation (9%-48% vs 0%-13%). There were no severe adverse events after POEM; 1 patient with pneumatic dilation sustained a perforation that was treated with endoscopic suturing. The above mentioned RCT reported comparative outcomes at 2 years following POEM and PD. There was higher treatment success at the 2-year follow-up in the POEM group (58 of 63 patients [92%]) than in the pneumatic dilation group (34 of 63 patients [54%]) (absolute difference, 38% [95% CI, 22%-52%]; P < .001; risk ratio, 1.71 [95% CI, 1.34-2.17]. Reflux esophagitis was observed significantly more frequently in patients treated with POEM than with PD (22 of 54 patients [41%] in the POEM group, of whom 19 [35%] were assigned LA grade A-B and 3 [6%] were assigned LA grade C, vs 2 of 29 [7%] in the PD group, all of whom were assigned LA grade A; absolute difference, 34% [95% CI, 12%-49%]; P = .002).[152]

Treatment outcomes in different achalasia subtypes

In the initial description of the 3 subtypes of achalasia based on high-resolution manometry, it was noted that the response to available treatments at the time (botulinum toxin injection, pneumatic dilation, and laparoscopic Heller myotomy) was best for achalasia type II and worse for type III.[6] This was corroborated by subsequent studies, with success rate ranges of 90% to 100% for type II, 63% to 90% for achalasia type I, and 33% to 70% for type III.[7-9] These findings were further confirmed in a meta-analysis of 9 studies that included 298 patients treated with pneumatic dilation and 429 patients who underwent laparoscopic Heller myotomy, showing that the best and worst outcomes were for patients with type II and III achalasia, respectively: type I versus type II after pneumatic dilation (OR, .16; 95% CI, .08-.36; P = .000), type I versus type III after pneumatic dilation (OR, 3.64; 95% CI, 1.55-8.53; P = .003), type II versus type III after pneumatic dilation (OR, 27.18; 95% CI, 9.08-81.35; P = .000), type I versus type II after laparoscopic Heller myotomy (OR, .26; 95% CI, .12-.56; P = .001), type I versus type III after laparoscopic Heller myotomy (OR, 1.89; 95% CI, .80-4.50; P = .148), and type II versus type III after laparoscopic Heller myotomy (OR, 6.86; 95% CI, 2.72-17.28; P = .000).[153]

There is a paucity of information regarding response to POEM in achalasia type III. An uncontrolled study of 32 achalasia type III patients treated with POEM reported treatment success (Eckardt score ≤3) in 90.6% after a median follow-up of 24 months.[154] Although data are limited, POEM has been recommended as the preferred treatment for achalasia type III both in a recent American Gastroenterological Association Clinical Practice Update[155] and an expert international consensus statement.[156]

Patient values and preferences and cost-effectiveness

Currently, no data exist regarding patient preferences with regard to various treatment strategies for the management of achalasia. Several recent studies have evaluated the cost-effectiveness of current management options in the treatment of achalasia.[157-159] Miller et al[159] performed a cost comparison including botulinum toxin injection, pneumatic dilation,

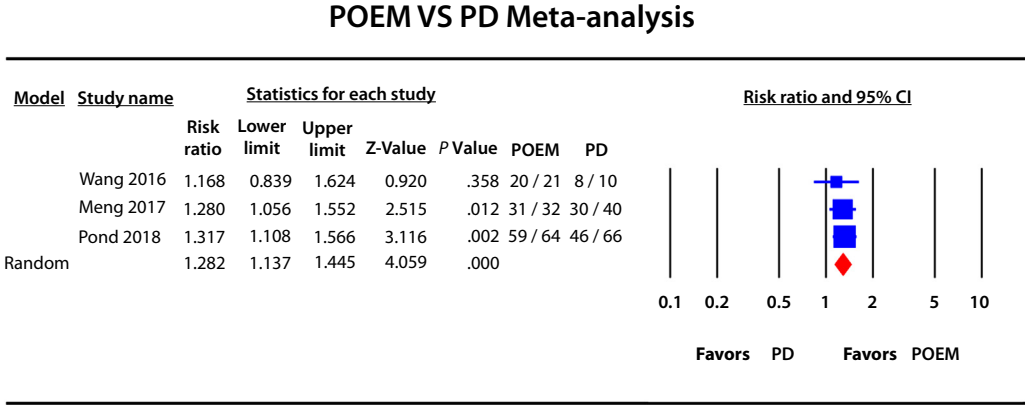

Figure 3. Forrest plot of clinical success between peroral endoscopic myotomy versus pneumatic dilation. *POEM*, Peroral endoscopic myotomy; *PD*, pneumatic dilation; *CI*, confidence interval.

laparoscopic Heller myotomy, and POEM based on single-institution data over a period of 4 years using cost-utility and cost-per-cure analysis, where "cure" was defined as patient being in remission and symptom free. Cost per cure for botulinum toxin injection for year 1 was $7862 and remained stable over 3 years but doubled to $14,986 from year 4 onward, attributed to higher treatment failure rates and need for reinterventions. In contrast to botulinum toxin, pneumatic dilation, laparoscopic Heller myotomy, and POEM were found to be more cost-effective over a 4-year follow-up duration. Cost per cure for pneumatic dilation was $7175 in the first year and was reduced to $2393 at year 4. Both laparoscopic Heller myotomy and POEM had similar cost per cure trends over year 1 to year 4 ($11,582 to $2896 and $12,120 to $3030, respectively). Pneumatic dilation was the most cost-effective strategy over a short-term follow-up of 2 years. However, pneumatic dilation was noted to have clinical efficacy of only 67% at year 3 compared with clinical efficacy of 90% for myotomy at year 3, and thus myotomy was noted to be most cost-effective over long-term follow-up.[159] Two additional economic evaluation studies suggested that pneumatic dilation may be the most effective approach over the short period, but it is associated with more diagnostic testing, reinterventions, and hospitalizations compared with myotomy.[157,158]

FUTURE DIRECTIONS

Final results from multiple randomized trials, including trials comparing POEM versus laparoscopic Heller myotomy and anterior versus posterior POEM, are awaited. Although existing results are very encouraging, POEM remains an intricate endoscopic procedure that requires advanced endoscopic skills, knowledge of surgical anatomy, and expertise in submucosal endoscopy and management of adverse events, such as bleeding, perforation, and leakage.[114] Multiple studies have evaluated the learning curves associated with this procedure.[160] Liu et al[161] found that 100 cases were required to decrease the risk of technical failure, adverse events, and clinical failure. Another single-center study demonstrated that endoscopists with experience in esophageal endoscopic submucosal dissection reached a plateau in POEM learning after approximately 25 cases.[162] In another single-center retrospective study, El Zein et al found that the minimum threshold number of cases required for an expert interventional endoscopist performing POEM was 13 cases.[163] Therefore, reported learning curve results for POEM vary widely between studies. This is likely because of different methodologies used to assess the learning curve and differences in operator experience.

No standardized training curriculum for POEM and submucosal endoscopy currently exists. With the increasing adoption of POEM as a first-line treatment modality for achalasia as well as a growing list of expanding indications, there is a need for effective training methods for both endoscopists in training and those already in practice. Currently, there are no data with regard to patient preferences over various treatment strategies, and studies carefully evaluating patient preferences are needed. The cost-effectiveness of POEM as compared with both pneumatic dilation and laparoscopic Heller myotomy is yet to be determined. Finally, quality indicators using relevant process and outcome measures need to be established.

CONCLUSIONS

Pneumatic dilation and laparoscopic Heller myotomy are effective and established treatment options in the management of achalasia patients. Since the introduction of POEM in 2008, this procedure has gained worldwide acceptance as a primary treatment for patients with achalasia and other esophageal motility disorders. Multiple studies and meta-analyses have reported its excellent efficacy and safety during the short- and medium-term follow-up, and recent literature suggest long-term efficacy as well. Short-term outcomes are at least equivalent to laparoscopic Heller myotomy, although the risk of gastroesophageal reflux could be higher. Severe adverse events are rare when the procedure is performed by experienced operators.

Recommendations

1. Laparoscopic Heller myotomy, pneumatic dilation, and POEM are effective therapeutic modalities for patients with achalasia. Decision between these treatment options should depend on achalasia type, local expertise, and patient preference. ⊕⊕⊕⊕
2. We recommend against the use of botulinum toxin injection as definitive therapy for achalasia patients. Botulinum toxin injection may be reserved for patients who are not candidates for other definitive therapies. ⊕⊕⊕◯
3. We suggest POEM as the preferred treatment for management of patients with type III achalasia. ⊕◯◯◯
4. In patients with failed initial myotomy (POEM or laparoscopic Heller myotomy), we suggest pneumatic dilation or redo myotomy using either the same or an alternative myotomy technique (POEM or laparoscopic Heller myotomy). ⊕◯◯◯
5. We suggest that patients undergoing POEM are counseled regarding the increased risk of postprocedure reflux compared with pneumatic dilation and laparoscopic Heller myotomy. Based on patient preferences and physician expertise, postprocedure management options include objective testing for esophageal acid exposure, long-term acid suppressive therapy, and surveillance upper endoscopy. ⊕⊕◯◯
6. We recommend pneumatic dilation compared with botulinum toxin injection for patients with achalasia. ⊕⊕⊕⊕
7. We recommend that laparoscopic Heller myotomy and pneumatic dilation are comparable treatment options for management of patients with achalasia types I and II, and the treatment option should be based on shared decision-making between the patient and provider. ⊕⊕⊕◯
8. We suggest that POEM and laparoscopic Heller myotomy are comparable treatment options for management of patients with achalasia types I and II, and the treatment option should be based on shared decision-making between the patient and provider. ⊕⊕◯◯

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Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; EGJ, esophagogastric junction; EndoFLIP, endoluminal functional lumen imaging probe; LES, lower esophageal sphincter; OR, odds ratio; POEM, peroral endoscopic myotomy.

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*Drs Khashab, Vela, and Thosani contributed equally to this article.

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Current affiliations: Division of Gastroenterology and Hepatology, Johns Hopkins Hospital, Baltimore, Maryland, USA (1), Division of Gastroenterology, Mayo Clinic Arizona, Scottsdale, Arizona, USA (2), Interventional Gastroenterologists of the University of Texas, Department of Internal Medicine, McGovern Medical School, Houston, Texas, USA (3), Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas, USA (4), Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California, USA (5), Division of Gastroenterology/Hepatology, University of California, San Diego, San Diego, California, USA (6), Section of Pediatric Gastroenterology, Baylor College of Medicine; Texas Children's Hospital, Houston, Texas, USA (7), Division of Digestive and Liver Diseases, Cedars-Sinai Medical Center, Los Angeles, California, USA (8), The Permanente Medical Group, Department of Gastroenterology, Kaiser Permanente San Francisco Medical Center, San Francisco, California, USA (9), Digestive Disease Institute, Virginia Mason Medical Center, Seattle, Washington, USA (10), Department of Gastroenterology, Kaiser Permanente San Francisco Medical Center, San Francisco, California, USA (11), Division of Gastroenterology and Hepatology, University of Iowa Hospital & Clinics, Iowa City, Iowa, USA (12), Department of Gastroenterology, Archbold Medical Group, Thomasville, Georgia, USA (13), Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA (14), Division of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA (15), Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA (16).

Reprint requests: Mouen A. Khashab, MD, Johns Hopkins Hospital, 700 Abell Ridge Circle, Towson, MD 21204.

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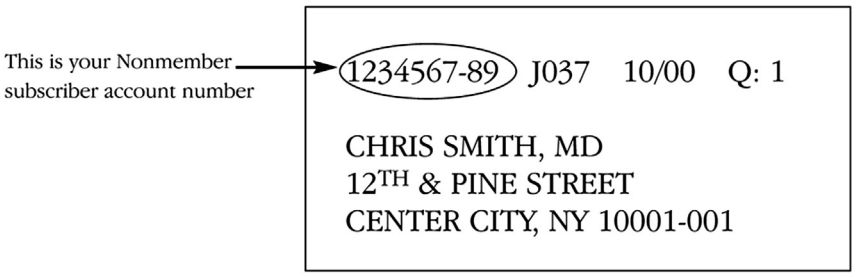
Sample mailing label



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APPENDIX 1. SEARCH STRATEGIES

Achalasia: botulinum toxins—final search strategy

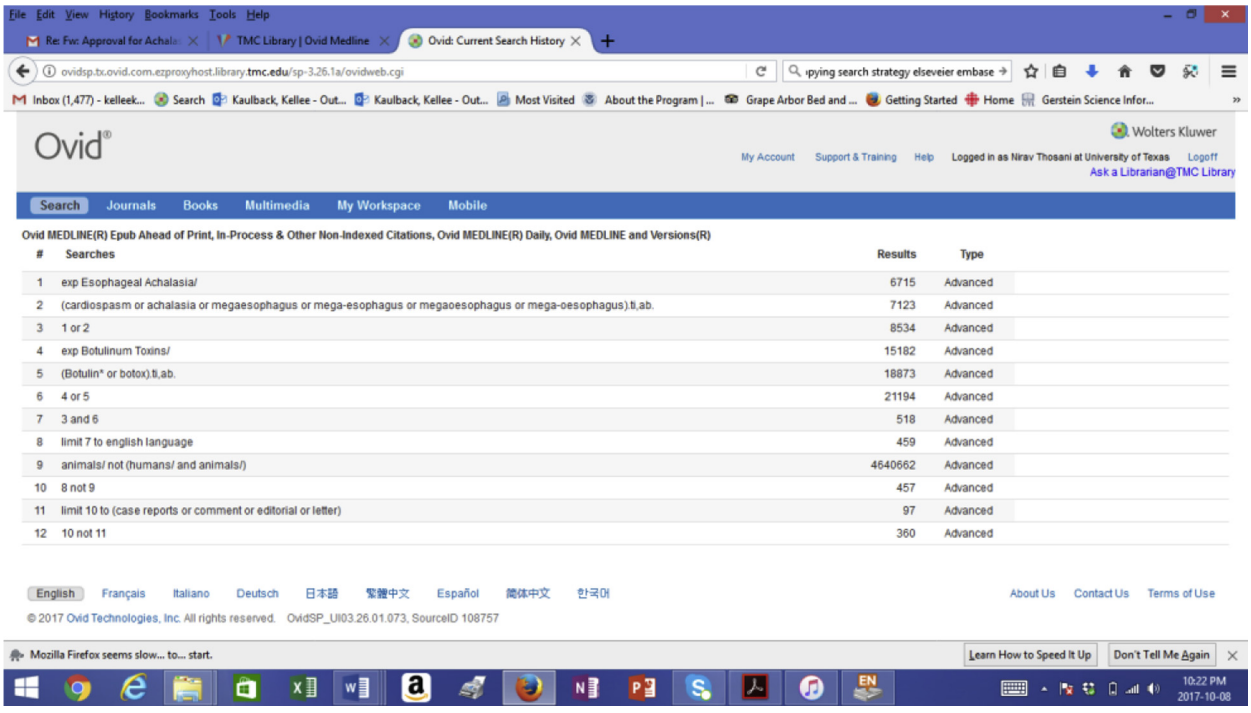
Search date: October 8, 2017

Databases searched: Ovid Medline(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R); Embase (Elsevier); Wiley Cochrane Library

Ovid Medline

Ovid Medline(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R)

#	Searches	Results
1	exp Esophageal Achalasia/	6715
2	(cardiospasm or achalasia or megaesophagus or mega-esophagus or megaoesophagus or mega-oesophagus).ti,ab.	7123
3	1 or 2	8534
4	exp Botulinum Toxins/	15,182
5	(Botulin* or botox).ti,ab.	18,873
6	4 or 5	21,194
7	3 and 6	518
8	limit 7 to english language	459
9	animals/ not (humans/ and animals/)	464,0662
10	8 not 9	457
11	limit 10 to (case reports or comment or editorial or letter)	97
12	10 not 11	360

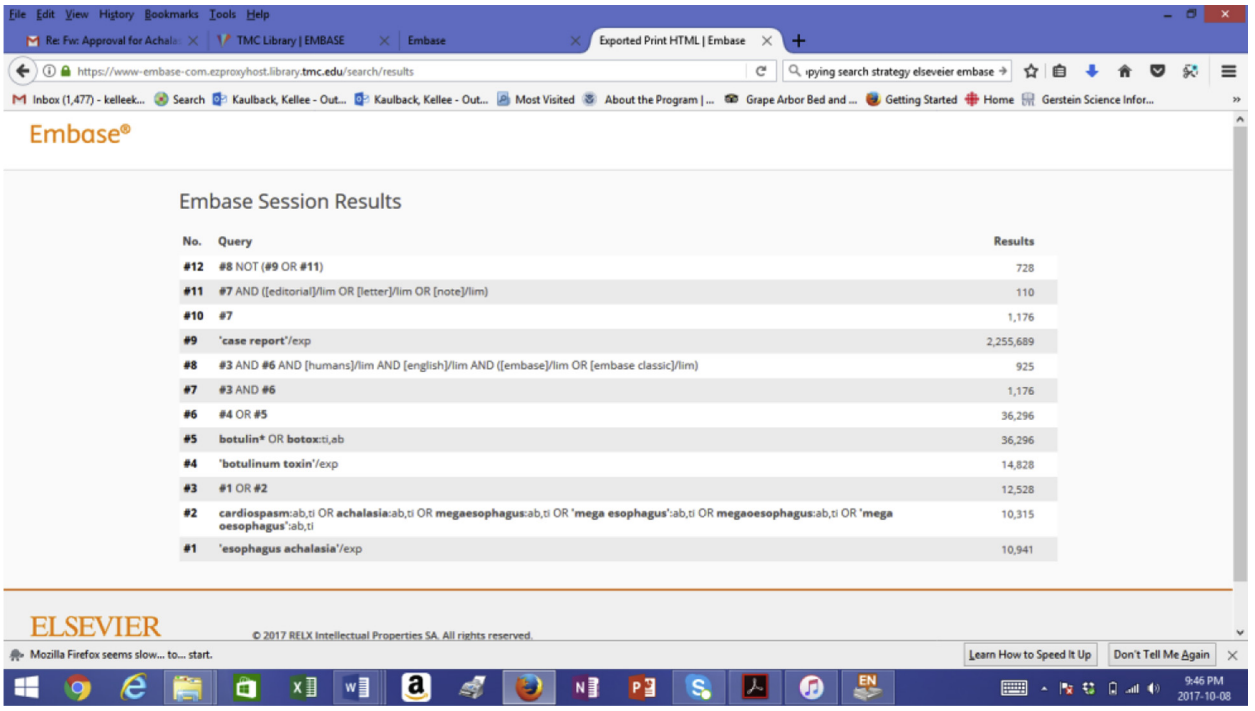


Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Esophageal Achalasia] explode all trees	111
#2	(cardiospasm or achalasia or megaesophagus or mega-esophagus or megaoesophagus or mega-oesophagus):ti,ab	226
#3	#1 or #2	231
#4	MeSH descriptor: [Botulinum Toxins] explode all trees	1154
#5	(Botulin* or botox):ti,ab	2178
#6	#4 or #5	2289
#7	#3 and #6	64

Elsevier Embase

Query((('esophagus achalasia'/exp) OR (cardiospasm:ab,ti OR achalasia:ab,ti OR megaesophagus:ab,ti OR 'mega esophagus':ab,ti OR megaoesophagus:ab,ti OR 'mega oesophagus':ab,ti)) AND (('botulinum toxin'/exp) OR (botulin* OR botox:ti,ab)) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)) NOT (('case report'/exp) OR ((('esophagus achalasia'/exp) OR (cardiospasm:ab,ti OR achalasia:ab,ti OR megaesophagus:ab,ti OR 'mega esophagus':ab,ti OR megaoesophagus:ab,ti OR 'mega oesophagus':ab,ti)) AND (('botulinum toxin'/exp) OR (botulin* OR botox:ti,ab))) AND ([editorial]/lim OR [letter]/lim OR [note]/lim)))



Achalasia: dilation—final search strategy

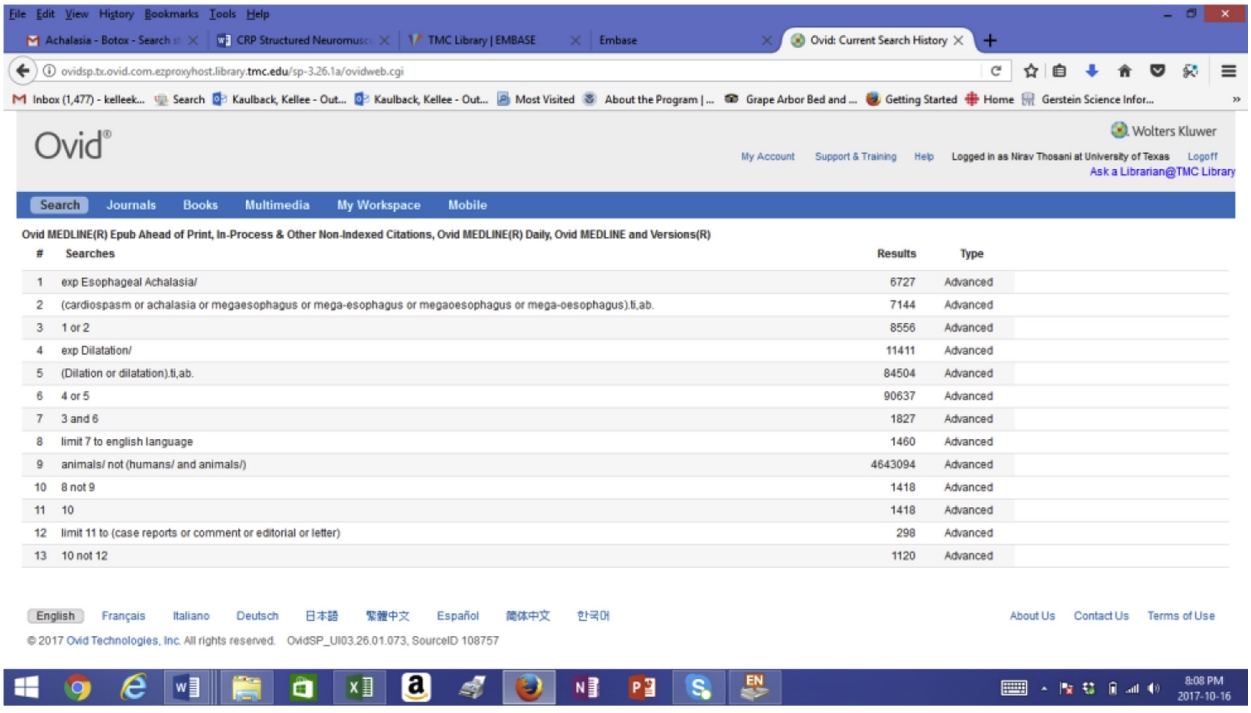
Search date: October 16, 2017

Databases searched: Ovid Medline(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R); Embase (Elsevier); Wiley Cochrane Library

Ovid Medline

Ovid Medline(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R)

#	Searches	Results
1	exp Esophageal Achalasia/	6727
2	(cardiospasm or achalasia or megaesophagus or mega-esophagus or megaoesophagus or mega-oesophagus).ti,ab.	7144
3	1 or 2	8556
4	exp Dilatation/	11,411
5	(Dilation or dilatation).ti,ab.	84,504
6	4 or 5	90,637
7	3 and 6	1827
8	limit 7 to English language	1460
9	animals/ not (humans/ and animals/)	4,643,094
10	8 not 9	1418
11	10	1418
12	limit 11 to (case reports or comment or editorial or letter)	298
13	10 not 12	1120



Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Esophageal Achalasia] explode all trees	111
#2	(cardiospasm or achalasia or megaesophagus or mega-esophagus or megaoesophagus or mega-oesophagus):ti,ab	226
#3	#1 or #2	231
#4	MeSH descriptor: [Dilatation] explode all trees	409
#5	(dilation or dilatation):ti,ab	5713
#6	#4 or #5	5872
#7	#3 and #6	103

Elsevier Embase

Query((((’esophagus achalasia’/exp) OR (’cardiospasm’:ab,ti OR ’achalasia’:ab,ti OR ’megaesophagus’:ab,ti OR ’mega esophagus’:ab,ti OR ’megaoesophagus’:ab,ti OR ’mega oesophagus’:ab,ti)) AND ((’balloon dilatation’/exp) OR (dilation OR dilatation:ab,ti)) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)) NOT ’case report’) NOT ((((’esophagus achalasia’/exp) OR (’cardiospasm’:ab,ti OR ’achalasia’:ab,ti OR ’megaesophagus’:ab,ti OR ’mega esophagus’:ab,ti OR ’megaoesophagus’:ab,ti OR ’mega oesophagus’:ab,ti)) AND ((’balloon dilatation’/exp) OR (dilation OR dilatation:ab,ti)) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)) NOT ’case report’) AND ([editorial]/lim OR [letter]/lim OR [note]/lim)

Achalasia: myotomy—final search

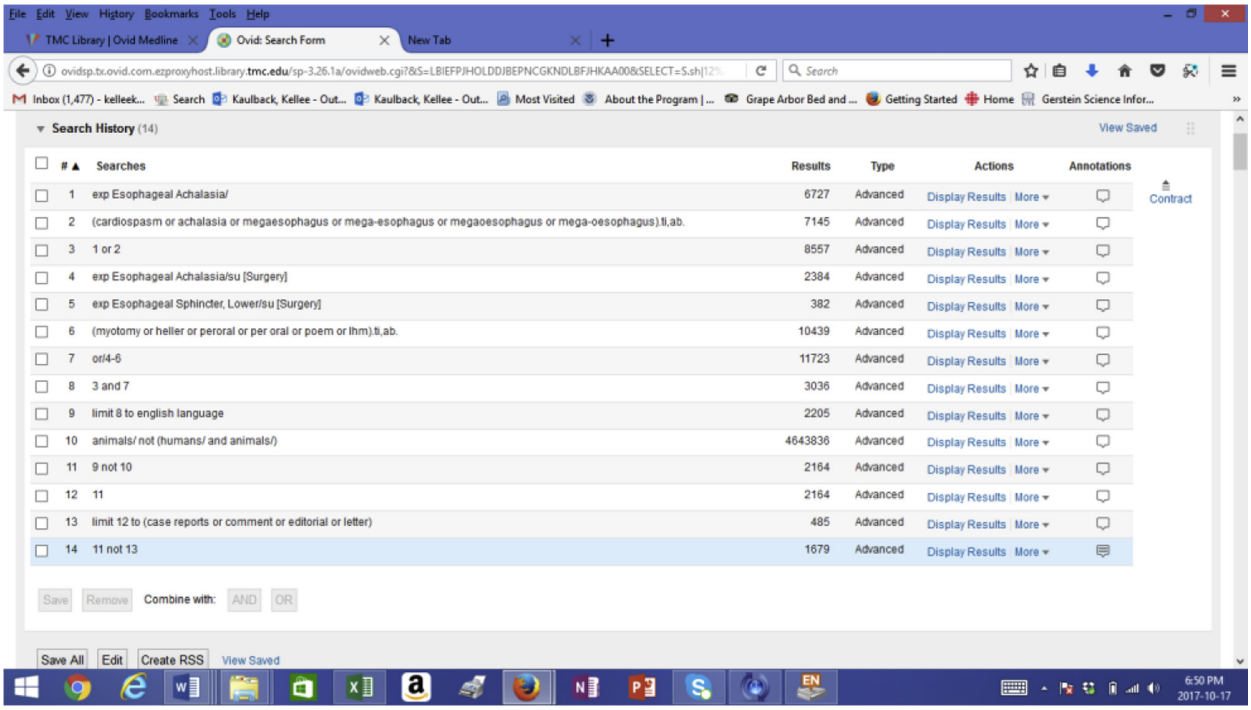
Search date: Oct 16-17, 2017

Databases searched: Ovid Medline(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R); Embase (Elsevier); Wiley Cochrane Library

Ovid Medline.

Ovid Medline(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily, Ovid Medline and Versions(R)

#	Searches	Results
1	exp Esophageal Achalasia/	6727
2	(cardiospasm or achalasia or megaesophagus or mega-esophagus or megaoesophagus or mega-oesophagus).ti,ab.	7145
3	1 or 2	8557
4	exp Esophageal Achalasia/su [Surgery]	2384
5	exp Esophageal Sphincter, Lower/su [Surgery]	382
6	(myotomy or heller or peroral or per oral or poem or lhm).ti,ab.	10,439
7	or/4-6	11,723
8	3 and 7	3036
9	limit 8 to English language	2205
10	animals/ not (humans/ and animals/)	4,643,836
11	9 not 10	2164
12	11	2164
13	limit 12 to (case reports or comment or editorial or letter)	485
14	11 not 13	1679



Embase

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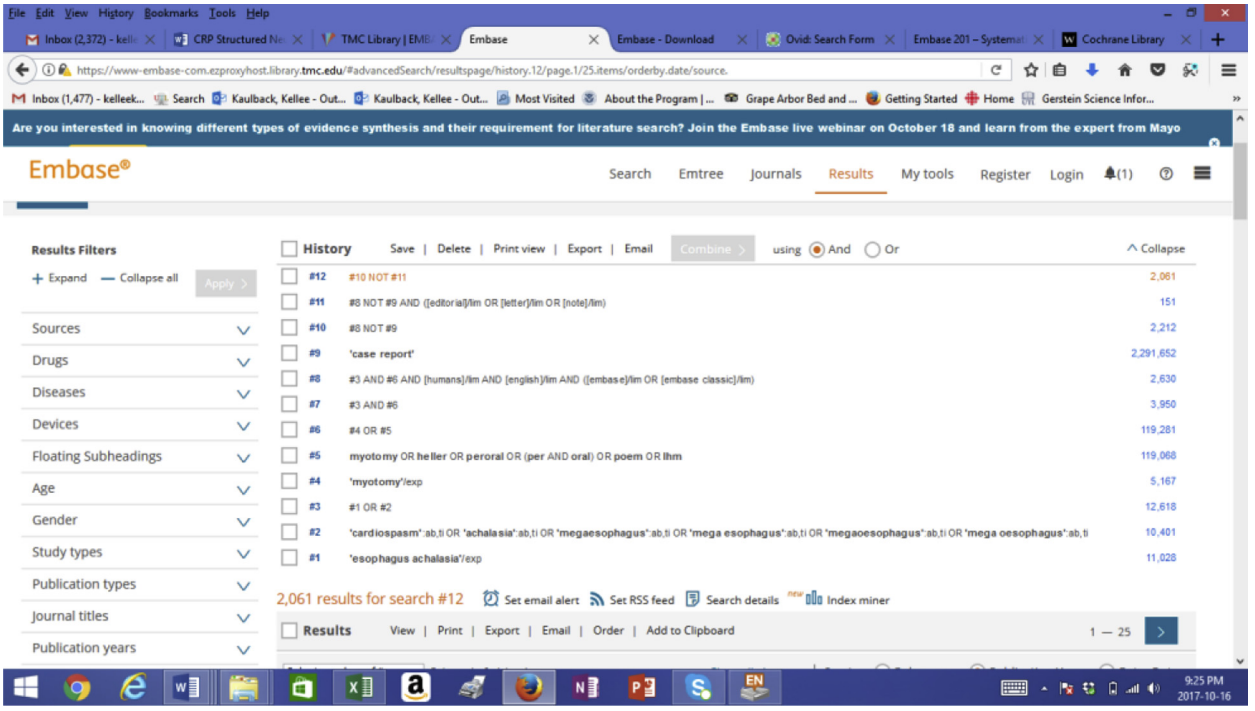

Wiley Cochrane Library

#1	MeSH descriptor: [Esophageal Achalasia] explode all trees	111
#2	(cardiospasm or achalasia or megaesophagus or mega-esophagus or megaoesophagus or mega-oesophagus):ti,ab	226
#3	#1 or #2	231
#4	MeSH descriptor: [Esophageal Achalasia] explode all trees and with qualifier(s): [Surgery - SU]	38
#5	MeSH descriptor: [Esophageal Sphincter, Lower] explode all trees and with qualifier(s): [Surgery - SU]	7
#6	(myotomy or heller or peroral or per oral or poem or lhm):ti,ab	8540
#7	#4 or #5 or #6	8553
#8	#3 and #7	114