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Systematic review with meta-analysis: endoscopic dilation is highly effective and safe in children and adults with eosinophilic oesophagitis

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Summary

Background: Oesophageal dilation is frequently used as an adjunct treatment to alleviate symptoms that develop from fibrostenotic remodelling in eosinophilic oesophagitis (EoE). Earlier reports described an increased risk of complications associated with dilation.

Aim: Perform a systematic review and meta-analysis to assess the efficacy and safety of endoscopic dilation in children and adults with EoE.

Methods: Professional librarians searched MEDLINE, EMBASE, the Cochrane library, Scopus, and Web of Science for articles in any language describing studies of dilation in EoE through December 2016. Studies were selected and data were abstracted independently and in duplicate. Random effects modelling was used to generate summary estimates for clinical improvement and complications (haemorrhage, perforation, hospitalisation, and death).

Results: The search resulted in 3495 references, of which 27 studies were included in the final analysis. The studies described 845 EoE patients, including 87 paediatric patients, who underwent a total of 1820 oesophageal dilations. The median number of dilations was 3 (range: 1-35). Clinical improvement occurred in 95% of patients (95% CI: 90%-98%, I^2: 10%, 17 studies). Perforation occurred in 0.38% (95% CI: 0.18%-0.85%, I^2: 0%, 27 studies), haemorrhage in 0.05% (95% CI: 0%-0.3%, I^2: 0%, 18 studies), and hospitalisation in 0.67% (95% CI: 0.3%-1.1%, I^2: 44%, 24 studies). No deaths occurred (95% CI: 0%-0.2% I^2: 0%, 25 studies).

Conclusions: Endoscopic dilation is consistently effective in children and adults with EoE, resulting in improvement in 95% of patients with very low rates (<1%) of major complications.

1 | INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic inflammatory disorder of the oesophagus, which is increasingly reported in children and adults.[1,2] This condition is considered a particular form of food allergy, in which proton pump inhibitor (PPI) therapy, topical steroids and specialised diets are effective in inducing and maintaining disease remission.[3-9] EoE has become the most common cause of dysphagia and food impaction in young adults.[10,11] Over time, features of oesophageal remodelling develop leading to a diffusely narrow calibre oesophagus and dominant strictures which may cause persistent dysphagia and require oesophageal dilation.[12-15]

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

Despite no impact on oesophageal inflammation, oesophageal dilation is one of the most effective options in the management of dysphagia of EoE patients with fibrostenotic features.[16] Earlier reports on performing dilation in patients with EoE described a higher than expected rate of complications, making dilation a less attractive approach in EoE.[17-20] Several more recent studies, however, have reported dilation to be a safe procedure.[21-23] In a previous meta-analysis, we found that major complications occurred in <1% of EoE patients undergoing dilation and that 75% of patients experienced clinical improvement.[16] The meta-analysis was limited to a relatively small number of studies and was restricted to an adult population. Since then, multiple centers have published data on dilation in EoE,[24-26] including recent studies on paediatric cohorts.[27-29]

To expand on and update our previous publication, we performed a systematic review and meta-analysis assessing the efficacy and safety of endoscopic dilation in children and adults with EoE.

2 | METHODS

We used PRISMA methodology for conducting this systematic review and meta-analysis.[30] This meta-analysis was registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42016037658). There was no funding received for this review.

2.1 | Selection criteria

To be included in this review, studies needed to involve adult or paediatric EoE patients undergoing oesophageal dilation. Major complications needed to be explicitly reported, as did clinical effectiveness. Major complications were defined as perforation, haemorrhage, hospitalisation, or death. Randomised controlled trials, prospective cohorts, retrospective observational studies, case series, and case reports were eligible for inclusion. Systematic reviews, guidelines, review articles, letters to the editors, editorials, and articles not relevant to EoE were excluded. Studies providing duplicate information, to include subsets of data already published, were excluded.

2.2 | Search strategy

A search of the literature was conducted by two of the authors (SC and LT), both professional librarians, in December 2016 without any restriction to language in the following databases: MEDLINE (via OvidSP, 1946 to present), EMBASE (via Elsevier, 1947 to present), and the Cochrane Library (via OvidSP), including Cochrane Register of Controlled Trials, through February 2016; the Cochrane Database of Systematic Reviews, 2005 to March 30, 2016; Database of Abstracts of Reviews of Effects, through 1st Quarter 2016; Health Technology Assessment, through 1st Quarter 2016; Cochrane Methodology Register, through 3rd Quarter 2016; and NHS Economic Evaluation Database, through 1st Quarter 2016. Literature search strategies in these databases used a combination of subject headings and index terms, as well as, key words relating to eosinophilic oesophagitis, endoscopic, dilation, Maloney, Savary, Through-the-scope, diameter, safety, perforation, haemorrhage, hospitalisation, chest pain, treatment outcomes, adverse events, complications and efficacy (full search strategy in Appendix S1). The main search strategy was conducted in MEDLINE. Parallel search strategies were conducted in EMBASE and the Cochrane Library. A third author (AL) searched Scopus, Web of Science, and abstracts from the most relevant gastroenterology and endoscopy conferences to include Digestive Diseases Week, American College of Gastroenterology, and United European Gastroenterology Week.

All references were screened for eligibility both independently and in duplicate. Two review teams, which included two authors on each team (JM/AL and FM/KD), each screened half of the references by review of titles and abstracts. If either reviewer on a team felt that a title or abstract suggested study eligibility, the full text of the reference was retrieved. The authors resolved any discrepancies by discussion.

2.3 | Data extraction

We developed a data extraction form for this study and each author agreed upon the variables a priori. All data were extracted independently and in duplicate to minimise error or bias. The variables included first author of the study, design of the study, year and country of publication, demographics (age, race, sex), clinical presentation (dysphagia, food impaction, heartburn, chest pain), allergic history (allergic rhinitis, food allergies, asthma, eczema), endoscopic features (rings, furrows, plaques, strictures), type of stricture (diffusely narrow, dominant, and location), treatment (PPI, steroids, diet), type of dilator used (Maloney, Savary-wire guided, through-the-scope balloon, Celestin, EndoFLIP (Endoluminal Functional Lumen Imaging Probe, Crospon, Inc, Carlsbad, CA, USA), or dilation with the endoscope, number of dilations performed per patient, clinical response and duration of response, patient follow-up, complications (perforation, haemorrhage, hospitalisation, death) whenever they were available. We also collected data on chest pain and mucosal laceration.

2.4 | Quality assessment

Studies were ranked according to three metrics of quality: study design, completion of follow-up, and duration of follow-up. We assigned a score of high for randomised controlled trials, moderate for cohort studies, and low for case reports and case series. For completion of follow-up, we assigned a score of high quality if more than 80% of patients had follow-up, moderate quality if between 50% and 80% had follow-up, and low if less than 50% had follow-up or if follow-up was not reported. For duration of follow-up, high quality studies reported follow-up greater than 6 months, studies that reported follow-up between 1 and 6 months were moderate in quality, and low quality was assigned if follow-up was less than 1 month. We considered a study to be of high quality overall if it

scored highly on all three metrics and low quality if it scored low on any metric (Tables S1 and S2).

2.5 | Endpoints

The primary outcomes of this meta-analysis were to assess the safety of dilation in EoE patients by calculating the rate of complications associated with dilation and to assess clinical improvement following dilation. Our secondary outcome was to explore whether differences existed in complication rate by type of dilator [Maloney, Savary, Through-the-scope (TTS) Balloon].

2.6 | Statistical analysis

Percentages of patients experiencing an outcome of interest were summarised with the aid of a random effects model for proportions (STATA command metaprop one).[31] The STATA command metaprop one was used to model outcome data. This routine provides procedures for pooling proportions in a meta-analysis and displays the results in a forest plot. The pooled estimate is obtained as a weighted average by fitting the logistic-normal random-effects model without covariates but random intercepts after Freeman-Tukey Double Arcsine Transformation to stabilise the variances.[32] The confidence intervals were based on the exact binomial (Clopper-Pearson) procedure.[33] For sparse event data, breakdown of the modelling procedure is known to occur, in which case calculation of the pooled estimate and confidence interval using the exact binomial method was performed. Statistical significance of heterogeneity was tested by means of the Chi-squared statistic for the likelihood ratio test. Heterogeneity was also quantified using the *I*-squared measure assigning categories of low, moderate, high or very high for values of 1%-25%, 26%-50%, 51%-75% and 76%-100% respectively.[34] Because methods for assessing publication bias in meta-analytic studies of proportion data are not well-established, we do not present such an analysis.[35,36]A sensitivity analysis was performed with regard to quality by excluding all case series and case reports.

All analyses were carried out using STATA (version-13.1; Statcorp, College Station, TX, USA). There was no funding received for this meta-analysis and all authors approved the final version of the manuscript.

3 | RESULTS

After removal of 989 duplicates, a total of 3495 potential articles were identified. Of these studies, 3435 number were excluded by title and abstract review. The full text of the remaining 60 articles was retrieved and reviewed, upon which it was determined that 27 studies met inclusion criteria (Figure 1).

Of these 27 studies, one was a randomised controlled trial,[25] two were prospective cohorts,[37,38] 16 were retrospective cohort studies,[17,21,23,24,26-29,39-47], two were case series and six were case reports.[19,46,48-53] All of the studies were single-center, except for one which included two centers.[21] Details are presented in Table 1.

Overall, there were 2873 EoE patients, of which 1112 were children (<18 years). The mean age of patients in the studies was 32.5 years (SD: 11.8) with a range from 4 to 83 years. The mean percentage of male patients in the studies was 75.5% with a range of 65% to 90%.

Rings were the most common endoscopic feature, reported in a mean of 73% of patients per study (range: 32%-100%, 18 studies) followed by furrows with a mean of 60% (range: 11%-93%, 12 studies) and white plaques with a mean of 47% (range: 3%-73%, 14 studies).

All studies reported a frequency of dysphagia, with 19 studies reporting dysphagia in 100% of patients. The mean percentage of dysphagia in the remaining studies was 82% (range: 29%-96%, eight studies).[17,23,24,29,40-43] Food impaction was reported in 59% of patients (range: 9%-100%, 20 studies), heartburn in 22% (range: 7%-56%, 15 studies), chest pain in 10% (range: 0%-33%, 13 studies).

The most common medical treatment used was topical steroids (mean: 58%, range: 6%-100%, 15 studies), followed by PPI (mean: 56%, range: 12%-100%, 16 studies), and diet (mean: 12%, range: 0%-23%, 8 studies).

Among the studies, 845 EoE patients (87 children) underwent a total of 1820 oesophageal dilations with a median of three dilations per patient with a range from 1 to a maximum of 35 dilations per patient.[26] The method of dilation included 110 Maloney, 454 Savary, 768 TTS balloon, 20 Celestin, two EndoFLIP[49,52] and one with an upper endoscope.[17] Some studies reported the minimum target diameter achieved, which ranged from 15 to 20 mm.[21,26,28,29,37,40,41,45-48,50-53] Among the eight studies that reported oesophageal diameter before and after dilation, the mean pre-dilation lumen diameter was 9.9 mm (SD: 2.0) and the mean post-dilation diameter was 16.1 mm (SD: 2.8). Of all 27 studies, only two did not explicitly report the presence of stricture.[26,37] Eight studies described the oesophageal stricture location, which was most commonly found distally (73.6%), followed by proximally (14.6%), and then (11.6%) in the mid-oesophagus.[25,27,38,43,45,49,51,53]

Clinical improvement from dilation occurred in 95% of EoE patients following dilation (95% CI: 90%-98%, I^2: 10%). Clinical response was similar between children (95% CI: 0.83-1.00, I^2: 8.6%, 3 studies) and adults (95% CI: 0.89-0.99, I^2: 15, 14 studies) (Figure 2). The duration of improvement was reported in 13 studies and with a median of 12 months and a range from 1 week to 36 months.[21,24,26-28,37,39,40,46,49-51,53] Follow-up rates exceeded 80% in all these studies except for 1, in which follow-up was 53%.[40] Sensitivity analysis conducted by excluding case series or case reports did not significantly alter the results (Figure 2).

Complications after dilation were rare. Perforations occurred in 0.38% (7/1831) (95% CI: 0.18-0.85 I^2: 27%, 27 studies), haemorrhage in 0.05% (1/1746) (95% CI: 0-0.3%, I^2: 0, 18 studies), and hospitalisation in 0.67% (12/1777) (95% CI: 0.3%-1.1%, I^2: 44%, 24 studies). There were no deaths reported in the studies (0/1831) (95% CI: 0-0.002, I^2: 0, 27 studies) (Figure 3). Significant

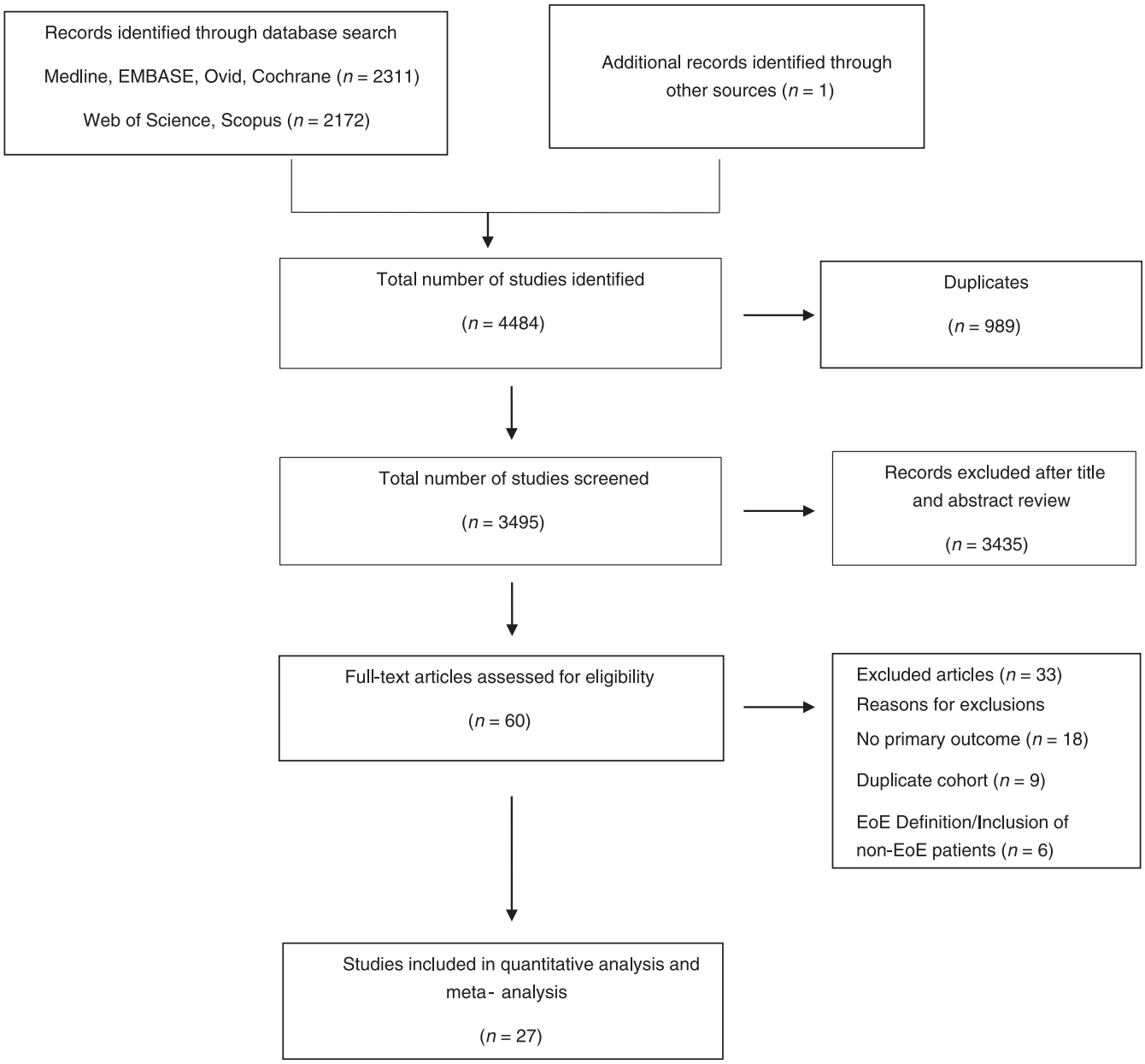

FIGURE 1 Flow chart for the systematic review

heterogeneity was found for perforation (*P*=.097) and for hospitalisation (*P*=.01). Due to the event outcomes rarely occurring, stratified analysis could not be performed for major complication events between children and adults.

Chest pain not requiring hospitalisation was reported in the majority of studies and occurred in 9.3% of patients (142/1513) with a wide variation between studies ranging from 0.63% to 100%. When stratified by age, chest pain following dilation occurred in similar frequency between children (95% CI: 0.00-0.43, I^2: 76%, four studies) and adults (95% CI: 0.00-0.22, I^2: 94%, 15 studies) (Figure S2). In the Schoepfer study, chest pain was self-reported in 74% and considered mild, but noted in only 7% of their existing medical records.[21] There was a wide variation in the definition of laceration in the studies from mucosal disruptions following dilation to deep mucosal tears and therefore a summary estimate could not be calculated. Mucosal laceration following dilation was reported in as low as 0.6% of patients[26] and up to 100% of patients.[27]

Due to the low overall complications, data were insufficient to compare the frequency of major complication rates between the three major types of dilators (Maloney, Savary, TTS).

4 | DISCUSSION

This systematic review and meta-analysis was performed to assess the clinical efficacy and safety of dilation in EoE. Our previous meta-analysis was limited to a relatively small number of studies and strictly to an adult population.[16] Since then, several other centers

TABLE 1 Characteristics for each study included in meta-analysis

Study	Study type	Total EoE patients	EoE patients dilated	Total # of dilations	Dilator type and # with each dilator	Mean age (years)	Clinical improvement (%)	Duration of follow-up (months)	Quality of Studies
Al-Hussaini 2016	Retrospective	50	10	19	Savary 19	9	100	36	Moderate
Ally 2011	Retrospective	196	54	66	Savary 29 Maloney 24 TTS 13	43	NR	NR	Low
Bohm 2010	Prospective	16	9	11	Savary 3 Maloney 6 NR 2	41	80	22	Moderate
Cantu 2005	Case series	2	2	3	Celestin 3	34	100	11	Low
Cohen 2007	Retrospective	36	9	NR	Maloney 2 TTS 5 Endoscope 1	34	NR	NR	Low
Croese 2003	Retrospective	31	17	58	Celestin 17 Remainder NR	34	94	NR	Low
Dhalla 2012	Retrospective	19	19	21	TTS 21	NR	NR	NR	Low
Dugan 2012	Case report	1	1	3	Savary 1 NR 2	51	NR	NR	Low
Eisenbach 2006	Case report	1	1	1	NR	17	NR	NR	Low
Enns 2010	Retrospective	54	15	15	NR	44	80	12	Low
Jung 2011	Retrospective	161	161	293	Savary 77 TTS 216	44	NR	NR	Low
Kavitt 2015	Randomised controlled	31	17	17	Maloney 17	NR	94	NR	Moderate
Lenglinger 2014	Case report	1	1	1	Esoflip 1	19	100	0.25	Low
Lipka 2014	Retrospective	95	13	157	Savary 10 Maloney 11 TTS 2 Remainder NR	30	100	24	Moderate
Lirio 2015	Case report	1	1	1	Esoflip 1	17	NR	NR	Low
Menard-Katcher 2015	Retrospective	781	40	68	Maloney 49 TTS 19	14	86	NR	Moderate
Pasha 2007	Retrospective	42	18	18	Savary 1 Maloney 1TTS 12 NR 4	44	85	NR	Low
Potter 2004	Retrospective	29	13	13	Savary 12 TTS 1	35	54	3	Low
Rajagopalan 2009	Case report	1	1	2	Savary 2	30	100	6	Low
Remedios 2006	Prospective	26	11	15	NR	36	NR	NR	Moderate
Robles-Medranda 2010	Retrospective	13	4	13	TTS 13	16	100	36	Moderate
Runge 2016	Retrospective	509	164	486	Savary 91 TTS 395	39	85	12	Moderate
Saligram 2014	Retrospective	30	30	30	Savary 30	33	NR	NR	Moderate
Schoepfer 2010	Retrospective	681	207	476	Savary 161 TTS 46 Remainder NR	44	93	15	Moderate
Seeger 2014	Case report	1	1	1	TTS 1	34	100	6	Low
Ukleja 2014	Retrospective	61	22	28	Savary 4 TTS 24	49	NR	NR	Moderate
Vasilopoulos 2002	Case series	4	4	4	Savary 4	25	100	12	Low

NR, not reported; TTS, through-the-scope balloon.

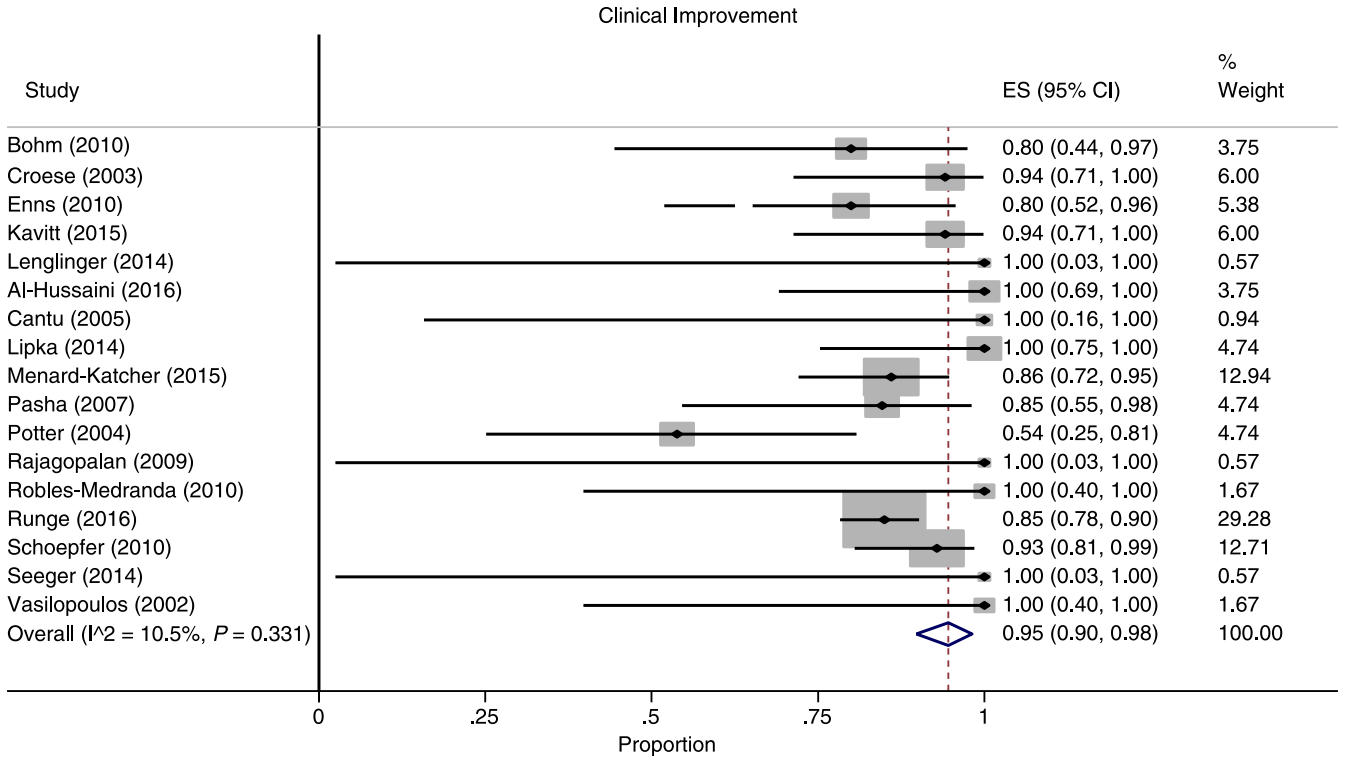

FIGURE 2 Forest plot for clinical outcomes including all studies. With inclusion of all studies, the summary effect for clinical improvement was 95%, I^2: 10%. After excluding case report and case series, summary effect was 90%, I^2: 32% (Figure S1)

have published their data on complications rates with dilation, including the first paediatric series. Patients who have undergone dilation have more than doubled and a threefold increase in endoscopic procedures has been observed since our previous meta-analysis. We demonstrated that dilation was highly effective in improving dysphagia. The frequency of major complications, which consisted of perforation, haemorrhage, hospitalisation, or death, was rare and occurred in well below 1% of patients.

Our aim was to assess the clinical efficacy of dilation in EoE and dilation was found to improve symptoms in 95% of patients. One of the earliest studies by Straumann et al. followed the natural history of 30 patients with EoE, 11 of whom were treated with dilation.[54] Clinical improvement was observed in 91% patients. Several more recent studies with a larger population of patients have also demonstrated efficacy. In the study by Runge et al. in which 164 EoE patients were dilated, 85% achieved clinical response.[24] Compared to our previous meta-analysis, the effectiveness rate has increased by 15% and importantly, heterogeneity in clinical improvement has dropped from 86% to 10%, hinting at a highly consistent effectiveness among recent studies published over the past 3 years.

Stricture formation is a consequence of long-term untreated or under treated EoE.[12] Studies have demonstrated that length of delay in diagnosis correlates with the presence of fibrostenotic features.[12,13] Endoscopic dilation does not impact the underlying inflammation and should be combined with an anti-inflammatory therapy. Since topical steroids and diet have shown their ability to reverse fibrotic remodelling,[55–57] it is plausible to speculate whether anti-inflammatory therapies may also reverse endoscopic features like strictures and narrow calibre oesophagus. This has been recently shown in small series or case reports and should be further explored.[58,59]

Initial case reports and small studies cautioned endoscopists about dilation in that was a newly encountered cause of food impaction and strictures.[19,20,60] Reports of perforation surfaced, as did the dramatic appearance of mucosal shearing following dilation or passage of an endoscope.[18,61] A large number of institutional studies is now available in children and adults. These include prospective cohorts and one randomised controlled trial demonstrating safety of dilation with a complication rate comparable to dilation for other types of oesophageal strictures.[62]

In our review, we only found seven cases of perforation out of a total of 1820 dilations, which were reported in three studies. One study was a retrospective design at a single institution which resulted in three perforations from 293 dilations, a second was an audit on endoscopic complications from dilations from a tertiary care center in which three perforations occurred, and the final perforation was reported in a case report of a 17-year-old woman. We excluded cases that had perforation reported by history as we wanted to ensure endoscopic dilation was the actual cause rather than spontaneous perforation from a delayed food disimpaction.[17] In our review, there was only one case of haemorrhage reported following dilation and there was not a single death reported.

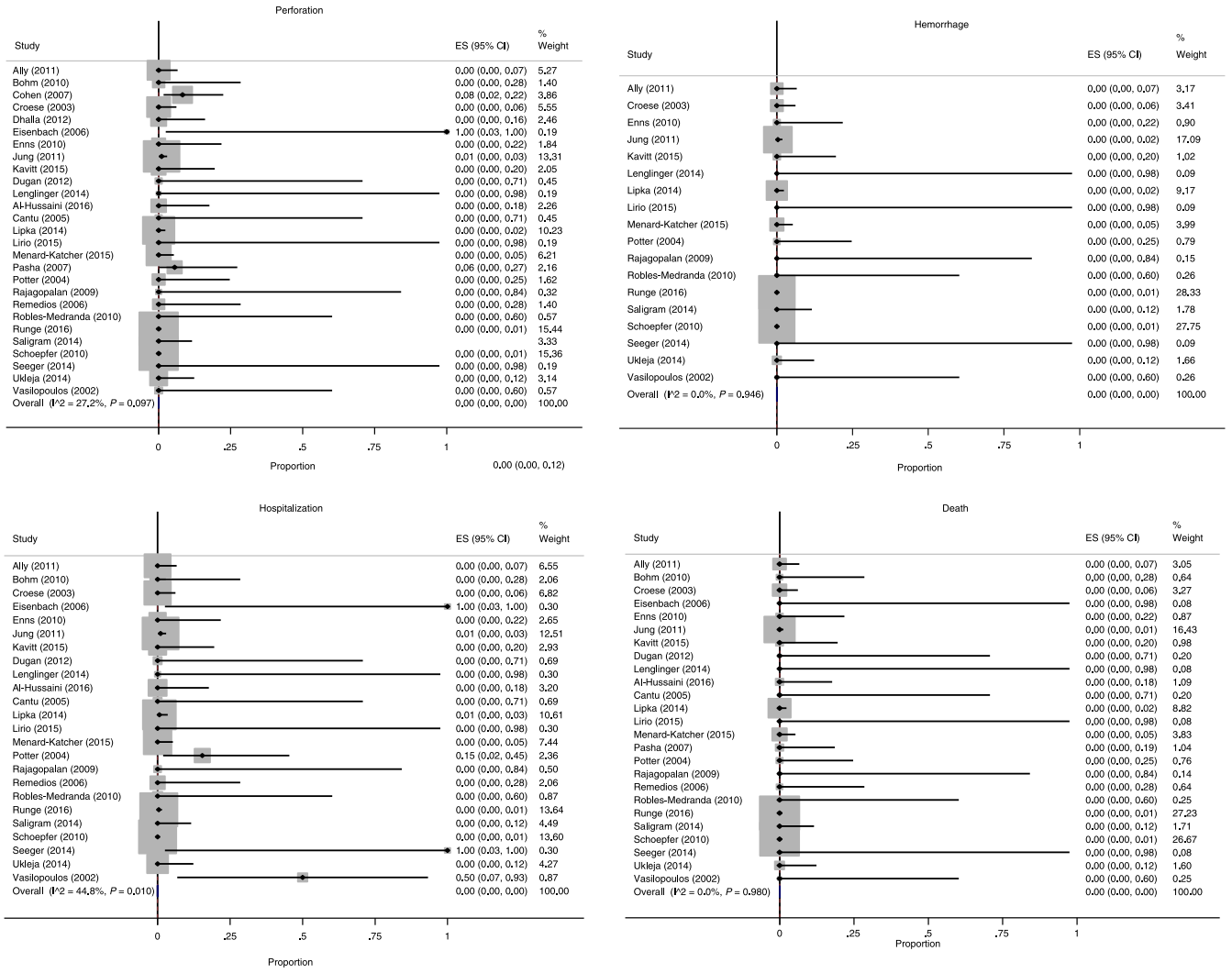

FIGURE 3 Forest plot for the frequency of the four major complications with dilation

The most frequent complication reported in studies exploring the safety of dilation in EoE was mucosal laceration. However, it is noteworthy that mucosal lacerations or even deeper rents are not actually complications, but rather the intended outcome of dilation and patients may not experience clinical improvement unless a tear develops. Given the variation in studies describing this feature, we were not able to calculate a summary effect. In addition, mucosal laceration is likely underreported as second-look endoscopy is not always performed following Savary or Maloney dilation. With mucosal tears of the oesophageal mucosa, post-procedural chest pain may develop. This is also most likely an underreported finding that patients may not seek medical attention for pain and endoscopists may not follow-up with patients within the days after dilation. Among the studies included, 9% of patients experienced chest pain, however less than 1% required hospitalisation for pain management. The only study to demonstrate a discrepancy between chest pain found in patient records versus in a post-procedural survey was by Schoepfer et al.[21] While medical records documented chest pain in only 7% of cases, in actuality, it occurred in 74% of patients, albeit mild. In most cases, this pain is self-limited, and can be managed with topical analgesics.

In our review, two cases were dilated with EndoFLIP, which has shown that reduced oesophageal distensibility can increase risk of food impaction, regardless of eosinophilic inflammation,[63] EndoFLIP may accurately identify patients with recurrent food impaction or dysphagia and therefore may identify candidates for oesophageal dilation. Whether the addition of this tool will enhance our understanding of dysphagia in EoE and refine our indications for endoscopic dilation remains to be elucidated.

Last, one of our aims was to explore whether factors can predict improvement in symptoms. Some studies reported a target oesophageal diameter following dilation, however, the data were not sufficient to obtain a summary estimate. We also wanted to compare the safety and efficacy of the three types of dilators, but given the limited number of studies with very low number of events, we could not perform meta-regression.

Our meta-analysis has several strengths. We performed a comprehensive search strategy of all major databases, as well as, abstracts from major meetings, without any restriction to language. Professional librarians with experience in meta-analysis assisted us in our search strategy. All studies were screened by two teams in

duplicate and data abstraction was performed in duplicate as well to minimise bias. Our review included children and adults therefore making our results more generalisable to all EoE patients.

The major limitation of our review was the quality of evidence included. There was only one small randomised controlled trial and two prospective cohorts. The majority of studies were retrospective and case reports, therefore, we were not able to grade the quality of studies included. This is particularly a limitation when attempting to assess clinical effectiveness of a procedure. The duration of follow-up after dilation was not reported in all studies and was limited to a relatively short period of time. We aimed to explore difference in types of dilators in complications and response, however, due to the limited number of studies with a low number of events, we could not compare differences.

In summary, oesophageal dilation is highly effective in improving clinical symptoms, at least in the short term, and is a safe procedure with a very low major complication rate.

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AUTHORSHIP

Guarantor of the article: Fouad J. Moawad

Author contributions: Fouad J. Moawad: study design, article selection, article retrieval, data abstraction, analysis, and interpretation, manuscript writing, approval of final version; Javier Molina-Infante: study design, article selection, article retrieval, data abstraction, analysis, and interpretation, manuscript writing, approval of final version; Alfredo Lucendo: study design, article search, article selection, article retrieval, data abstraction, analysis, and interpretation, manuscript writing; Sarah E. Cantrell: article search, article selection, manuscript writing, approval of final version; Lyubov Tmanova: article search, article selection, manuscript writing, approval of final version; Kevin M. Douglas: study design, article selection, article retrieval, data abstraction, analysis, and interpretation, statistical analysis, manuscript writing, approval of final version.

LINKED CONTENT

This article is linked to Moaward et al and Kia and Hirano papers. To view these articles visit https://doi.org/10.1111/apt.14216 and https://doi.org/10.1111/apt.14213.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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