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Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy

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SUMMARY

Eosinophilic esophagitis (EoE) is an increasingly recognized clinical entity. The optimal initial treatment strategy in adults with EoE remains controversial. The aim of this study was to employ a decision analysis model to determine the less costly option between the two most commonly employed treatment strategies in EoE. We constructed a model for an index case of a patient with biopsy-proven EoE who continues to be symptomatic despite proton-pump inhibitor therapy. The following treatment strategies were included: (i) swallowed fluticasone inhaler (followed by esophagogastroduodenoscopy [EGD] with dilation if ineffective); and (ii) EGD with dilation (followed by swallowed fluticasone inhaler if ineffective). The time horizon was 1 year. The model focused on cost analysis of initial treatment strategies. The perspective of the healthcare payer was used. Sensitivity analyses were performed to assess the robustness of the model. For every patient whose symptoms improved or resolved with the strategy of fluticasone first followed by EGD, if necessary, it cost an average of \$1078. Similarly, it cost an average of \$1171 per patient if EGD with dilation was employed first. Sensitivity analyses indicated that initial treatment with fluticasone was the less costly strategy to improve dysphagia symptoms as long as the effectiveness of fluticasone remains at or above 0.62. Swallowed fluticasone inhaler (followed by EGD with dilation if necessary) is the more economical initial strategy when compared with EGD with dilation first.

Keywords

cost analysis; decision analysis; eosinophilic esophagitis

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic¹ inflammatory condition of the esophagus with increasing incidence.^{2–4} It frequently leads to symptoms of dysphagia⁵ and a heightened risk of esophageal food impaction,^{6–9} and is most commonly diagnosed among those aged 20–50 years.¹⁰ Studies estimate that 10–15% of adults who undergo an upper endoscopy to evaluate dysphagia are diagnosed with EoE.^{11–13} As EoE is a relatively recently discovered condition, most therapies provided are empiric and based on a small number of studies in the literature.

There are very few prospective trials published to date evaluating first-line therapies for this condition among adult patient populations. One therapeutic approach, esophageal dilation, involves a standard outpatient upper endoscopy procedure, followed by empiric dilation using either a bougie dilator or a through-the-scope balloon dilator to stretch the esophagus. The most commonly used medical therapy for patients with EoE is to administer a corticosteroid metered-dose inhaler via swallowing.^{14–16} It has not yet been determined whether it is sufficient to treat this condition until symptoms of dysphagia resolve, or if histologic resolution of esophageal eosinophils is needed. Use of systemic corticosteroids¹⁷ has also been reported, as has use of leukotriene inhibitors¹⁸ and nebulized budesonide.^{19,20} However, currently the most common treatment strategies employed are swallowed fluticasone with or without esophageal dilation. In a recent retrospective study of 207 patients with EoE who had undergone esophageal dilation with or without antieosinophilic medication, the authors did not identify a significant difference in symptomatic improvement between the groups.²¹ However, the symptom of dysphagia improved in both groups, suggesting effectiveness of both treatment options.

At this time there is a paucity of prospective controlled studies regarding the relative beneficial effect of various therapeutic options in patients with EoE, resulting in controversy regarding the optimal initial treatment option. This decision analysis intends to assess the costs associated with the common initial management strategies for EoE. Our primary research focus was to determine the least costly treatment strategy between the two most commonly employed options using a decision analysis model.

MATERIALS AND METHODS

We constructed a decision analysis model to determine the least costly initial treatment strategy to attain clinical resolution or improvement of dysphagia symptoms among adult patients diagnosed with EoE. We used a decision analysis software package (TreeAge Pro 2011 Suite; TreeAge Software Inc., Williamstown, MA, USA) to create a decision tree to compare the two most commonly employed strategies of fluticasone inhaler use and upper endoscopy with esophageal dilation. The cost analysis was performed from the perspective of a third-party payer, incorporating direct healthcare costs, over a 1-year time horizon. Costs were discounted to adjust for the study time horizon. Estimates of effectiveness were obtained from the existing literature. We conducted a literature review of all publications in Medline containing the term ‘eosinophilic esophagitis’ and assessed treatment options for

adult patients with this condition. We included the most clinically relevant and highest quality available studies.

Model assumptions and decision tree

The base-case patient was an adult patient with a history of dysphagia symptoms with biopsy-proven EoE who continues to be symptomatic despite proton-pump inhibitor therapy. Figure 1 depicts an abbreviated version of the decision tree. A patient with previously diagnosed EoE (meeting the criteria of 15 or more eosinophils per high-powered field taken from biopsies of the mid-esophagus) who remains symptomatic despite proton-pump inhibitor therapy could initially undergo either a 6-week course of swallowed fluticasone metered-dose inhaler (at a dose of 880 mcg twice daily; Strategy A), or an upper endoscopy with esophageal dilation (Strategy B). The duration of 6 weeks of fluticasone administration was used in the model as this is the duration of therapy utilized in relevant studies of adult patients.^{22,23} A dose of 880 mcg twice daily was used in the model as this is what was used in a randomized placebo-controlled trial in adults²⁴ and is consistent with our clinical practice.

Oral candidiasis was considered the main clinically significant complication of fluticasone inhaler use in the model. As is common in clinical practice, our model assumed that if dysphagia symptoms persisted, a subsequent upper endoscopy with dilation was pursued.

In patients with EoE undergoing upper endoscopy with dilation, the decision model incorporated two possible clinically significant complications: bleeding requiring endoscopic hemostasis or esophageal perforation. All cases of reported perforation after esophageal dilation have only required inpatient observation and intravenous antibiotics (over a mean hospital stay of 5.3 days) without the need for surgical intervention, as we have depicted in the model.²⁵ Using the TreeAge software, package rollback was performed. One-way and two-way sensitivity analyses were carried out to assess the robustness of the model by varying all assumptions included in the decision analysis tree over a clinically reasonable range of possibilities.

RESULTS

Model probabilities

Each strategy in the model is supported by evidence-based probabilities of effectiveness and probabilities of complications from the literature (Table 1). As the model focused on determining which treatment to use first, and the alternative treatment strategy was employed if the initial treatment strategy failed, the overall effectiveness was expected to be equivalent in both arms. Thus the model effectively focused on cost analysis of the initial treatment strategies.

Model cost estimates

Standard market charges for a patient paying the retail cost of prescription medication, without insurance coverage for pharmaceuticals, were obtained from <http://www.drugstore.com> and are shown in Table 2. Charges to the Center for Medicare and

Medicaid Services for outpatient endoscopic procedures and corresponding professional fees were obtained from a compilation of Center for Medicare and Medicaid Services physician fee schedule, RVU files, and the Federal Register. Charges to Medicare for relevant inpatient stays (following complications of esophageal dilation) were obtained from our institution's assistant director of finance and corporate decision support, and reflect the typical Medicare reimbursement in our region (Table 2).

Cost analysis

In patients with EoE, the strategy of fluticasone first followed by esophagogastroduodenoscopy (EGD), if necessary, cost an average of \$1078 per patient to attain symptomatic improvement or resolution, compared with an average cost of \$1171 for the strategy of EGD with dilation employed first. One-way sensitivity analyses performed over clinically reasonable ranges for all variables found that the model was only sensitive to changes in the probability of effectiveness of fluticasone (Fig. 2a). One-way sensitivity analysis indicated that EGD with dilation becomes, on average, the more economical choice of therapy if the effectiveness of fluticasone in improving or resolving dysphagia symptoms dropped below 0.62 (Fig. 2a). Two-way sensitivity analysis similarly indicated that if probability of dysphagia resolution was more than 0.62, then fluticasone would be the preferred strategy; while below this effectiveness, EGD with dilation first would be the more beneficial approach (Fig. 2b). The model was otherwise fairly robust across all ranges tested.

DISCUSSION

To our knowledge, this is the first decision analysis model to attempt to determine the most economical initial therapeutic option in the management of adults with EoE. We found that swallowed fluticasone inhaler (followed by EGD with dilation if necessary) is the less costly strategy when compared with EGD with dilation first. If the effectiveness of fluticasone in improving or resolving symptoms falls below 62%, EGD becomes the more economical initial strategy. The best estimate from the published literature to date illustrates that fluticasone has an effectiveness of 70% of improving dysphagia symptoms.²⁷ Until further prospective studies are performed comparing the role of dilation versus fluticasone, this decision analysis model suggests use of fluticasone as first-line therapy (followed by EGD if fluticasone fails) should be the initial approach.

EoE is a disease of increasing incidence, prevalence, and awareness, and can cause significant symptoms of dysphagia. Clinical decisions regarding first-line treatment options for EoE are generally based on data from small, retrospective studies.^{22,23,28} A recent review of the literature suggested 70% likelihood of symptom improvement post fluticasone therapy.²⁷ A wide range of symptomatic relief among adult patients receiving fluticasone is reported in the literature, ranging from 100%²² to 50%.²⁸ As an intermediate figure of 70% has been used as a previously accepted figure in the literature,²⁷ we chose this as a value to input into our model. It is important to acknowledge this wide range of reported impact on symptoms, as a randomized placebo-controlled trial among adults²⁴ did not observe a statistically significant difference in symptomatic improvement between those receiving

fluticasone and those receiving placebo. We utilized a sensitivity analysis with a full range of possibilities of effectiveness (from 0–100%) to account for this uncertainty. Furthermore, it is likely that a dose response to fluticasone exists, and future prospective studies are needed to compare symptomatic response with a range of doses.

For EGD with dilation, we employed a 93% probability of effectiveness based on a 2010 retrospective study in which 63 patients with EoE were treated with dilation alone. This study found that post dilation, 48% of patients reported no further dysphagia and 45% reported only slight dysphagia.²¹ However, given less than robust previous data on effectiveness of both therapies, we employed the use of sensitivity analysis in our decision analysis model accounting for the full range of probabilities (zero to one) for both therapies. Based on this model, if the therapeutic effectiveness of fluticasone therapy is perceived to be more than 62%, then this option would be the less costly approach as the initial treatment strategy in EoE.

Expert opinion regarding the initial choice between dilation versus fluticasone therapy in EoE is mixed. Recent 2011 consensus recommendations regarding EoE management highlight the need for future studies to clarify the specifics of topical corticosteroid therapy and the role of esophageal dilation, and do not delineate an algorithm for initial management between these two strategies.²⁹ Many gastroenterologists empirically perform esophageal dilation for patients with EoE; however, the main concern regarding this form of therapy had been the incorrect presumption that patients with EoE may be at increased risk (previously thought to be 5%) of perforation.^{29,30} This led to increasing use of fluticasone therapy as the initial treatment option. However, three recent studies indicate that esophageal dilation of EoE patients is a much safer endeavor than previously thought.^{21,25,26} Thus, we conducted this cost analysis to determine if one treatment option is preferable solely based on cost factors rather than fear of perforation. Decision analysis models are necessary to help guide decision making regarding first-line therapy until higher level evidence becomes available, and to highlight gaps in the literature to guide future research.

In this study we focused on data regarding treatment effectiveness in adult patients with EoE. Both the quantity and quality of studies regarding therapy for EoE are superior in the pediatric patient population compared with the adult patient population. However, in many ways pediatric EoE displays a clinical presentation and pathogenesis distinct from adult EoE, and it remains unclear if pediatric and adult populations have similar responses to the various therapeutic options available.³¹ We included only the two most common treatment options in adults, namely fluticasone inhaler and esophageal dilation. Nebulized budesonide^{19,20} was not considered because of limited use in clinical practice and the significant expense of budesonide inhaled suspension and a nebulizer delivery device, which would have resulted in the dismissal of this treatment option in a cost analysis model. Studies of other treatment options, including allergy testing, elimination diets, and oral viscous budesonide, were also not included because of limited published data in the adult population.

The model does have several limitations that must be taken into account. A decision analysis model such as this is not able to account for an individual patient's personal preferences

and/or attitudes toward risk, nor does it account for the risk aversion of their gastroenterologist. The model also does not address the durability of response, given the lack of reasonable quality data on the topic. Some studies have found limited durability and high recurrence rates for fluticasone therapy²³ and longer response rates for dilation.²¹ This may have an impact on the long-term symptomatic effect of these treatment modalities. Duration and durability of treatment options are not accounted for in the format of decision analysis model used and could be expected to have an impact on costs over time. Although the model utilizes the best evidence available, the studies cited are generally of small sample size and are retrospective. Furthermore, a wide range of cost possibilities for gastrointestinal bleeding and perforation after dilation exists depending on patient acuity, length of hospital stay, and whether or not an intensive care unit stay is indicated. However, the range of values utilized in each sensitivity analysis (as shown in Table 2) allows for these range of cost values to be taken into account.

In summary, this decision analysis model answers an important clinical question regarding the costs of initial management of EoE, suggesting a slight cost superiority of initial treatment with fluticasone. Given the paucity of controlled studies available, our model also suggests a need for high-quality, randomized controlled trials to assess therapeutic options for this increasingly prevalent condition.

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Fig. 1.
Decision analysis model.

Fig. 2.

Probability of symptom improvement post-fluticasone and/or dilation. **(a)** One-way sensitivity analysis. Blue squares indicate fluticasone inhaler $\times$ 6 week course and the pink diamonds indicate esophagogastroduodenoscopy (EGD) with dilation. **(b)** Two-way sensitivity analysis. The blue area indicates fluticasone inhaler $\times$ 6 week course and the green area indicates EGD with dilation.

Table 1

Baseline probabilities (range) employed in model

Probabilities		Base case (range)	References
Improvement/resolution of dysphagia	EGD with dilation	0.93 (0–1)	21,26
	Fluticasone	0.7 (0–1)	22,23,27,28
Potential complications	Perforation due to dilation	0.008 (0–0.05)	21,25,26,29
	Significant bleeding due to dilation	0.00119 (0–0.05)	21,25,26,29
	Oral candidiasis due to fluticasone	0.03125 (0–0.2)	23

EGD, esophagogastroduodenoscopy.

Table 2

Costs (\$US) employed in the model

	Cumulative charges to CMS (\$)	Range (\$)
EGD with dilation over guidewire (CPT 43248)	804 ^{†‡} (192 M.D. and 612 facility fees)	700–1900
EGD with control of bleeding, any method (CPT 43255)	900 ^{†‡} (288 M.D. and 612 facility fees)	700–1900
6-week course of fluticasone (220 mcg inhaler, 4 puffs swallowed twice daily)	740.97 [§]	500–1500
Nystatin oral suspension (60 cc bottle)	39.99 [§]	20–60
1-night inpatient admission for GI bleeding	14 733 [¶]	5000–30 000
5-night inpatient admission for esophageal perforation (not requiring surgical repair)	38 139 [¶]	10 000–100 000

CMS 2010 rates (Hospital outpatient payment + MD payment in-facility):

[†] PFS Relative Value File RVU11AR December 30, 2010. National Average Medicare physician payment rates calculated using a conversion factor of \$33.9764.

[‡] Source: November 24, 2010 Federal Register.

[§] Drugstore.com.

[¶] Source: Vanderbilt University Medical Center institutional finance officer.

CMS, Center for Medicare and Medicaid Services; CPT, current procedural terminology; EGD, esophagogastroduodenoscopy; GI, gastrointestinal.