

Beyond the Induction Phase: Should We Keep the Proton Pump Inhibitor in Pediatric Eosinophilic Esophagitis?

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ABSTRACT **Background:** Proton pump inhibitors (PPIs) are a common and effective management strategy for eosinophilic esophagitis (EoE) leading to successful remission in most cases. However, there is uncertainty regarding the ideal follow-up pharmacological treatment to maintain remission. We performed a cost-effectiveness and quality-adjusted life year (QALY) analysis.

Objectives: To compare various approaches of pharmacologic treatments for EoE.

Methods: A Markov model was constructed to evaluate the cost-effectiveness and QALY of maintenance therapies for eosinophilic esophagitis, including PPI, topical corticosteroids (tCS), and no treatment strategy, with crossover in treatments for primary and secondary nonresponse. The primary outcomes were incremental cost-effectiveness and QALY at a 5-year time horizon.

Results: In the base-case scenario (5-year time horizon), the average costs were no treatment: ₪73,075, PPI: ₪81,455, and tCS: ₪145,669 as maintenance therapy, with PPI being the dominant strategy (more effective/less costly), and a QALY of 4.5543, 4.5538, and 4.2283, respectively.

Conclusion: PPI was the most effective/least costly maintenance therapy. PPI is also the most cost-effective pharmacologic strategy. The relatively low adverse effects of this treatment, in addition to its effectiveness and low cost, make it an ideal choice following successful PPI induction treatment.

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KEY WORDS: cost-effectiveness, eosinophilic esophagitis (EoE), Markov model, proton pump inhibitors (PPI), quality-adjusted life year (QALY)

function and histologically by eosinophil-predominant inflammation [1,2]. The diagnostic criteria for EoE include clinical symptoms of esophageal dysfunction, eosinophilic infiltration of the esophageal mucosa with ≥ 15 eosinophils per high-power field, and exclusion of other disorders associated with esophageal eosinophilia [3].

EoE management focuses on symptom relief and histological remission with three main approaches: dietary modifications, pharmacological therapy, and endoscopic complication interventions [4-6]. Although elimination diets are highly effective, they face challenges of poor adherence, particularly in older children [7-9]. As a result, pharmacological options, such as proton pump inhibitors (PPIs), topical corticosteroids (tCS) [10] such as fluticasone or oral viscous budesonide, and biologic therapies such as dupilumab (anti-interleukin-4 α receptor), are utilized [11,12]. These treatments have different efficacy, side effects, and costs.

Since PPI treatment is often administered following esophagogastroduodenoscopy, even before a definitive histological diagnosis, to treat ailments such as dyspepsia or gastroesophageal reflux disease (GERD), it is commonly used as an induction treatment at a high dose [13]. While some guidelines support continuing PPI treatment [2,14], others do not perceive this to be an ideal treatment in EoE unless there is an overlap with GERD symptoms [15].

A recent analysis of cost-effectiveness in treatment-naïve EoE patients found PPI treatment to be the most cost-effective pharmacological treatment for EoE [16]. Since most patients start empirical PPI treatment before final biopsy results, it is important to evaluate the best empirical maintenance approach after successful PPI induction, considering quality-adjusted life year (QALYs) and cost-effectiveness.

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease of the esophagus characterized by symptoms of esophageal dys-

The objective of this study was to formulate a decision analysis model (Markov model) based on recently published data. This model analyzes the different medications while evaluating factors such as efficacy, side effects, cost-effectiveness, and QALYs.

PATIENTS AND METHODS

BASE CASE DEFINITION

The base case for this analysis was a hypothetical 12-year-old boy with newly diagnosed EoE who demonstrated a histologic and symptomatic response to an 8-week high-

dose PPI treatment. Response to treatment in our model was defined as no clinical symptoms and histology containing less than 15 eosinophils in a high-power field from at least six biopsies from three levels of the esophagus [1,2]. This representative case was chosen to reflect a common clinical scenario in pediatric practice, where a treatment decision must be made regarding maintenance therapy following successful PPI induction. The Markov model simulated long-term outcomes, costs, and QALYs over a 5-year horizon, evaluating three potential treatment strategies: discontinuing therapy (no treatment), continuing standard-dose PPI maintenance therapy with escalation to tCS in case of loss of response and subsequently to Dupilumab if tCS failed, and initiating maintenance with tCS followed by escalation to dupilumab due to treatment failure. At each stage, patients could either remain in response or transition to non-response health states, with potential progression to esophageal stricture requiring dilation. This model structure reflects contemporary clinical decision-making, accounting for therapeutic sequencing, and supports comparative evaluation of the cost-effectiveness of treatment strategies in pediatric EoE management.

The outcomes of interest were discounted QALYs, discounted lifetime costs, and the incremental cost-effectiveness ratio (ICER). The cycle length was 3 months with a 5-year time horizon. Health outcomes and costs were discounted by 3% annually. If a strategy was more expensive and less effective, then it was considered dominated. The model was analyzed from the perspective of the Israeli health system. The analysis was conducted according to the recommendations for conducting and reporting of cost-effectiveness analyses. The study followed a trusted, gold-standard set of guidelines published in 2016 by a group of expert scientists, revising the original (first panel) group recommendations of health economics guidelines from 1993. [17].

MODEL STRUCTURE

At each cycle, patients may remain in their response health state or transition to a no-response health state. In the no-response health state, patients may have an esophageal stricture and need an esophageal dilation.

Parameters used in the models are outlined in Table 1. Estimates for treatment response rates, and thereby state-transition probabilities, were obtained from the literature. State-transition probabilities were kept consistent between first, second, and third lines of therapy, given retrospective

Table 1. EoE treatment costs (₪)

Description	Value	Low	High
Cost of anesthesia	1721	1500	2000
Cost of biopsy	253	150	400
Cost of dupilumab	17,457	15,000	20,000
Cost of anesthesia, esophagogastroduodenoscopy, and biopsy	3622	0	3622
Cost of esophagus dilatation	8057	0	8057
Cost of esophagogastroduodenoscopy	1648	0	1648
Cost of PPI	129	100	200
Cost of tCS	3938	3000	4300
Disutility of esophageal stricture	-0.2	-0.1	0
Rate of esophagitis stricture1	0.172	0.15	0.2
Rate of esophagitis stricture2	0.308	0.25	0.35
Rate of esophagitis stricture3	0.39	0.3	0.5
Rate of response dupilumab	0.595	0.5	0.7
Rate of response placebo	0.02	0.01	0.03
Rate of response PPI	0.51	0.4	0.6
Rate of response tCS	0.649	0.55	0.75
Rate of maintenance	0.99	0.9	1
Annual discount rate	0	0	0.05
Time horizon (in quarters)	20	20	40
Utility of no response	0.89	0.21	0.23
Utility of response	0.96	0.22	0.25

All costs are reported in ₪

Rrate of esophagitis stricture1 is the rate of esophagitis stricture after 2 years of no response, esophagitis stricture2 after 5 years of no response, and esophagitis stricture3 after 20 of no response years

EoE = eosinophilic esophagitis, PPI = proton pump inhibitors, tCS = topical corticosteroids, ₪ = New Israel Shekel

cohort and clinical trial data, suggesting that second-line therapy histologic response rates do not differ significantly from first-line therapy rates. We assumed that the annual rate of loss of response (LOR) in patients who responded is 4%. Costs of pharmacologic therapy and the cost of esophagus dilation were obtained from the pricelist of the Ministry of Health in Israel. An annual discount rate of 3% was applied to all analyses. Utility values of health states were based on the literature and cost-effectiveness analysis registry of Tufts University [18].

Sensitivity analysis

One-way sensitivity analyses of all variables (Tornado diagram) and probabilistic sensitivity analyses were performed to assess the effect of uncertainty in modelling parameters on outcomes of the model. Sensitivity analysis evaluated variations in treatment response rates and costs as well as the utility of treatment response and non-response.

Data were collected and analyzed from October 2024 through June 2025. All analyses were performed with TreeAge Pro Suite 2025 Software (TreeAge Software Inc., Williamstown, MA, USA) and MATLAB (Math-Works, Inc. 2024b). Artificial intelligence was used to assist in rephrasing and improving the clarity and style of the manuscript. All scientific content was authored and verified by the authors.

ETHICS STATEMENT

As this research did not involve patient data or human subjects, institutional review board approval was not applicable.

RESULTS

The cost of no treatment strategy is ₪73,075, which is the lowest cost strategy with 4.2283 QALY. The continuing PPI standard dose strategy’s cost is ₪81,455 with 4.5543

QALY. The tCS strategy’s cost is ₪145,699 with 4.5538 QALY. The cost-effectiveness plan is shown in Table 1. The ICER of continuing PPI standard dose compared to no treatment strategy is ₪25,700 per QALY. The continuing PPI standard dose strategy dominates the tCS strategy (less cost and higher QALY). The ICER comparing tCS strategy to no treatment strategy is ₪223,029 per QALY. The ICER value is:

(Δcost / ΔQALY)

SENSITIVITY ANALYSIS

The tornado diagrams of continuing PPI standard dose compared to no treatment strategy, and tCS strategy compared to no treatment strategy, are presented in Figure 1A and 1B.

A one-way sensitivity analysis of the rate of response with PPI, as well as the rate of response with tCS, showed that even for a lower rate of 40%, the rate of response of tCS is 54%. The ICER is less than ₪60,000 per QALY in both cases, which is much less than the threshold of willing to pay (WTP) of ₪150,000 per QALY.

PROBABILISTIC SENSITIVITY ANALYSIS

The incremental cost-effectiveness scatter plot for WTP of ₪100,000 per QALY is presented in Figure 2.

DISCUSSION

This Markov model analysis demonstrates that PPI therapy is both more cost-effective and yields greater QALYs compared to tCS or to no treatment for patients with EoE. These findings, which are consistent with those of Hiramoto et al. [16], have important implications for clinical practice guidelines, healthcare resource allocation, and patient management strategies.

Our model revealed that at 5-year time horizon, PPI therapy was associated with slightly higher QALYs and

Table 2. Incremental cost-effectiveness ratio of the different treatment strategies

Strategy	Cost (₪)	ΔCost	QALY	ΔQALY	ICER
No treatment	73,075 ± 106		4.2283 ± 0.0005		
Continue PPI standard dose	81,455 ± 852	8380	4.5543 ± 0.0001	0.3261	25,700
tCS	145,669 ± 874	64,214	4.5538 ± 0.0001	-0.0006	Dominated

ICER = incremental cost-effectiveness ratio, PPI = proton pump inhibitors, QALY = quality-adjusted life year, tCS = topical corticosteroids, ₪ = New Israel Shekel

Figure 1. A tornado diagram assessing the effect of uncertainty in modelling parameters on outcomes of the model

ICER = incremental cost-effectiveness ratio, PPI = proton pump inhibitors, tCS = topical corticosteroid

[A] between the no treatment and continuing standard dose topical corticosteroids strategies

[B] Between no treatment and continuing proton pump inhibitors strategies

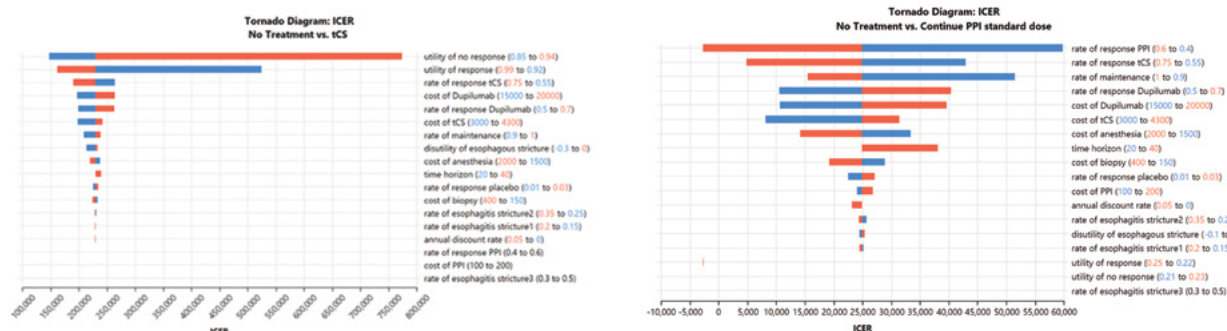
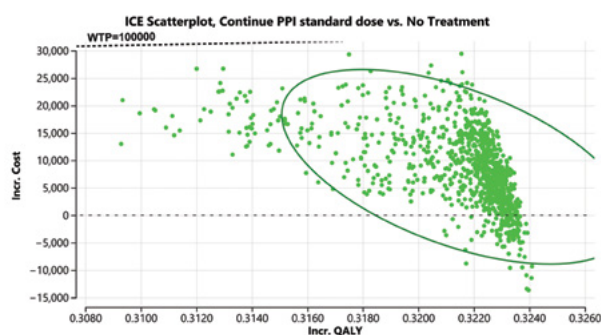


Figure 2. The incremental cost-effectiveness scatter plot for willingness to pay of ₪100,000 per QALY

Incremental cost-effectiveness scatterplot comparing PPI standard dose strategies to no treatment strategy on probabilistic sensitivity analysis

ICE = incremental cost-effectiveness, WTP = willingness to pay, ₪ = New Israeli Shekel, QALY = quality-adjusted life year, PPI = proton pump inhibitors



lower overall costs compared to topical corticosteroids. Specifically, PPI therapy resulted in a mean cost of ₪81,455 compared to ₪145,669 for topical corticosteroids, while simultaneously providing greater quality-adjusted survival. The ICER consistently favored PPI as the dominant strategy (more effective and less costly), making it the economically preferred first-line treatment option for EoE. The no treatment strategy, while avoiding initial medication costs, which did indeed lead to the lowest cost of ₪73,075, ultimately resulted in the poorest outcome in

terms of QALYs due to disease progression and complications requiring more intensive interventions over time. The reason that the no treatment strategy incurs the lowest cost could be a result of the relatively low price of endoscopies in Israel. Endoscopies are much more expensive in other countries, making this strategy less favorable in those nations, from a cost-effectiveness aspect.

Our results align with recent clinical evidence suggesting that PPI therapy is effective in inducing both clinical and histological remission in a substantial proportion of EoE patients [19]. The PPI-responsive phenotype of EoE has gained increasing recognition, with studies reporting response rates between 40% and 60% depending on the specific patient population and PPI regimen used [2]. Our model incorporated these response rates and demonstrated that even accounting for patients who did not respond to PPI following the initial successful PPI induction therapy, the overall cost-effectiveness remained favorable compared to alternative strategies.

Several factors likely contribute to the superior QALYs and cost-effectiveness profiles of PPI therapy. First, PPIs are generally less expensive than tCS, particularly when considering generic formulations. Second, the administration of PPIs is straightforward, potentially leading to better adherence compared to topical steroids, which require specific administration techniques to maximize esophageal deposition and minimize oral deposition or systemic absorption. Third, the safety profile of PPIs is well-established, with relatively low rates of serious adverse events during short- to medium-term use, although concerns about long-term use exist [20]. Since our model

is one of a 5-year time horizon, these are less relevant as is the possibility of higher rates of LOR, which do not seem to appear this early [19,20]. Last, the efficacy of PPIs in controlling both acid-related and inflammatory components of EoE pathophysiology may contribute to better symptom control and quality-of-life improvements, translating to higher utility values in our model.

The sensitivity analyses performed in our model revealed that the cost-effectiveness advantage of PPI therapy remained robust across a wide range of plausible parameter values. The variables with the greatest impact on model outcomes included PPI response rates, medication costs, and the utility values assigned to different health states. Even when these parameters were varied within clinically reasonable ranges, PPI therapy maintained its position as the most cost-effective strategy in most scenarios. This result suggests that our findings are likely to be applicable across diverse clinical settings and patient populations.

It is important to acknowledge that our model, like all Markov models, has certain limitations. First, the model assumes discrete health states that may not fully capture the spectrum of disease severity and symptom burden experienced by patients with EoE. Second, the utility values used were derived from literature and expert opinion rather than direct measurement in a large cohort of EoE patients, potentially limiting their accuracy. Third, the model does not account for potential long-term complications of PPI therapy, such as increased risk of fractures or micronutrient deficiencies, or the option of higher rates of LOR. These variables could affect the cost-effectiveness ratio if therapy is continued beyond the time horizons considered in our analysis. Last, the model does not fully capture the heterogeneity of EoE phenotypes and individual patient responses to different treatment modalities.

Despite these limitations, our findings have important implications for clinical practice. The superior cost-effectiveness of PPI therapy supports its use as a first-line treatment for EoE following initial PPI high-dose induction, particularly in healthcare systems with resource constraints. This finding aligns with recent guidelines that recommend PPI therapy as an initial approach for many patients with EoE [20]. However, it is crucial to emphasize that treatment decisions should be individualized and based on patient preferences, co-morbidities, and specific disease characteristics. For patients who fail to respond to PPI therapy or experience adverse effects, tCS remain an important treatment option despite the less

favorable cost-effectiveness profile.

From a healthcare system perspective, our findings suggest that formularies and coverage policies should ensure access to PPI therapy for patients with EoE, as these policies represent a cost-effective use of resources. In addition, the substantial difference in cost-effectiveness between active treatment and no treatment underscores the importance of early diagnosis and intervention in EoE to prevent disease progression and complications.

Future research should focus on refining predictive biomarkers for PPI responsiveness in EoE, which could further improve the cost-effectiveness of therapy by allowing more targeted treatment approaches. In addition, longer-term studies examining the durability of response to PPI therapy and the impact of maintenance therapy on disease outcomes would provide valuable data for extending our model to longer time horizons. Last, direct measurement of quality of life and utility values in large cohorts of EoE patients receiving different treatments would enhance the accuracy of future cost-effectiveness analyses.

CONCLUSIONS

Our Markov model demonstrates that PPI therapy provides greater QALYs at lower costs compared to topical corticosteroids or no treatment for patients with EoE. These findings support the use of PPI therapy as a first-line treatment strategy following successful initial PPI induction treatment for EoE from both clinical and economic perspectives. However, treatment decisions should ultimately be guided by a comprehensive assessment of individual patient factors, treatment goals, and shared decision-making between patients and healthcare providers.

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**Learning is acquired by reading books; but the much more necessary learning,
the knowledge of the world, is only to be acquired by reading man,
and studying all the various editions of them.**

Philip Dormer Stanhope, 4th Earl of Chesterfield (1694–1773), British politician, diplomat and writer

Capsule

Effect of screening with multicancer early-detection test on late-stage cancer diagnosis

Sasieni and colleagues reported major results from the NHS-Galleri randomized trial, examining whether a blood-based multicancer early-detection (MCED) test reduces late-stage cancer diagnoses. In England, 142,250 adults aged 50–77 years were randomized approximately equally to MCED testing plus usual care or usual care with stored blood samples. Blood sampling was performed at up to three annual screening rounds. The primary outcome was diagnosis of stage III or IV cancer among 12 prespecified cancer types. Contrary to the hoped-for effect, stage III–IV cancer incidence was not significantly reduced by MCED screening. The incidence-rate ratio was 1.03 (95%CI 0.92–1.14; $P=0.63$).

For the key secondary outcome of stage IV cancer alone, the incidence-rate ratio was 0.86 (95%CI 0.74–1.00). Thus, a possible reduction in stage IV disease was observed, but the primary endpoint was negative. Trial-related adverse events occurred in fewer than 1% of participants, and none were serious. The investigators emphasize that additional follow-up is required because stage shifts and their consequences may evolve over time. These findings therefore do not yet establish that adding this MCED blood test to usual screening reduces late-stage cancer overall.

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