Background: Elimination diets are used to treat eosinophilic esophagitis (EoE), with success (remission) defined at endoscopy and oesophageal biopsy as fewer than 15 eosinophils per high power field (HPF). Response is assessed after 6 weeks of treatment by convention, but we have observed that this period of time may be insufficient.

Objective: To characterise a subset of patients with EoE who require prolonged (>6 weeks) of dietary therapy to achieve histologic remission.

Methods: A retrospective search of electronic medical records of 2 cohorts with EoE attending the Department of Gastroenterology, University of Chapel Hill North Carolina, and Eastern Health, Melbourne Australia. Patients who underwent elimination diet, had esophageal biopsy after 6 or more weeks of dietary restriction that demonstrated ongoing esophageal inflammation (>15 eosinophils per HPF), and who then continued dietary therapy followed by repeat endoscopy demonstrating remission (<15 eosinophils per HPF) were included.

Results: Seven patients met inclusion criteria, average esophageal eosinophil counts prior to diet was 38.5 (range, 15–65). Following the initial period of diet (mean of 6 weeks and 4 days) eosinophil count decreased (average, 21.5/HPF; range 15–40/HPF). After extended dietary elimination (mean, 13 weeks; range, 7–22 weeks), histological resolution was achieved (average peak eosinophil count of 5.2; range, 0–14) in all cases. Endoscopic appearance and symptoms both improved following the initial period of dietary elimination, thereby preceding the histological resolution, and were sustained.

Conclusion: A subset of patients has full histologic response to prolonged elimination diet, that lags initial symptomatic and endoscopic improvement.

Keywords: Esophagitis; Eosinophil; Diet; Allergy; Histology; Endoscopy

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition thought to be caused by food and/or aeroallergen exposure [1]. Compelling evidence points to food antigens as the principle trigger, with multiple studies showing that elimination diets can resolve (and upon reintroduction, cause) the eosinophilic inflammatory infiltrate typical of EoE [2-5].
Therefore, elimination diet is advocated as a first line management strategy [6]. However, the duration of dietary therapy required to define success is arbitrary, may vary across treatment centres [4, 5], and there are no data examining the impact of different lengths of initial treatment on outcomes. Confirmation of treatment response requires endoscopy and oesophageal biopsy, but as there is no agreement on what level of oesophageal eosinophilia constitutes a histologic response, a variety of thresholds are employed, with some studies specifying a response as <15 eosinophils per high power field (HPF), and others choosing <5 eosinophils per HPF [7, 8]. Moreover, success of dietary therapies varies across centres, possibly directly because of this difference [9].

Clarification of the optimal duration of dietary elimination required to induce remission is of critical and immediate clinical relevance. Studies of elemental diet showed symptom improvements in less than 2 weeks, but analogous histologic data are not available and no data are available for empiric elimination diets [10]. Based on clinical experience, we postulate that longer durations of dietary elimination may lead to higher response rates and a greater percentage of patients who benefit from a nonpharmacological approach. The aim of this study, therefore, was to determine if prolonged (>6 weeks) dietary elimination can resolve eosinophilic infiltration of the oesophagus in patients with EoE who had a partial or incomplete initial response.

MATERIALS AND METHODS

The research was performed in 2 centres. First, the records of a group of patients previously enrolled in a prospective clinical study (including the 6 food elimination diet, avoiding gluten, dairy, egg, soy, fish/shellfish, and nuts) based in Melbourne Australia (between December 2013 and January 2016, and described in detail previously [2]) were searched. Second, at the University of Chapel Hill, North Carolina (UNC), Division of Gastroenterology and Hepatology, a retrospective chart review was conducted of all patients with a diagnosis of EoE presenting to the UNC, Division of Gastroenterology and Hepatology between the 1st of January 2011 and 1st of April 2017, who received elimination diet therapy followed by upper gastrointestinal endoscopy and biopsy, following a structured clinical algorithm described previously [11]. In addition, records of patients involved in an ongoing prospective study of dietary therapy guided by novel allergy tests (and thus avoiding a more limited number of food groups) were also interrogated. In all cohorts, electronic medical records were used to validate the identified subjects, and to collate physician records, endoscopy findings and histopathology reports. Demographic information (age, sex, body mass index), comorbidities, medications, duration of EoE and previous treatment of EoE were recorded. The date of index (diagnostic) upper endoscopy and biopsy, commencement of dietary therapy, subsequent endoscopy and biopsies, symptoms (defined by dysphagia, odynophagia or food bolus impaction events, and graded as absent, mild, moderate or severe by the treating clinician), endoscopic appearance (using the EoE endoscopic reference score – EREFS, as described previously, also see Table 1 and histology reports were noted [12, 13]). Histologic response (<15 eosinophils per HPF) was defined based on the clinical report of an expert pathologist. Only patients who had histologic evidence of active oesophageal eosinophilia (>15 eosinophils/HPF) after at least 6 weeks of dietary therapy, and who went on to receive an extended course of the initially prescribed dietary elimination followed by repeat oesophageal biopsy were included. The study was approved by the UNC Institutional Review Board (approval number: 17-1708), and
the ethics committee of Eastern Health, Melbourne Australia (E19/1213). All patients were consented in the required fashion.

**RESULTS**

Seven patients were identified who had a partial reduction in eosinophil count in response to an initial course of elimination diet, and following extended dietary elimination met histological criteria for response. Five patients from Chapel Hill, North Carolina (from a total of 68 attempting elimination diet), and 2 patients from Melbourne Australia (from 52 attempting elimination diet) had such a response, equating to 5.8% (7 of 120). This subset of patients is in addition to those responding to elimination diet at 6–8 weeks, with 29 of 52 (52%) response (Melbourne Australia), and 25 of 68 (37%) initially noted. Patient characteristics and temporality of treatment response are detailed in Tables 1 and 2 and Figs. 1 and 2 (subject numbers as described in Tables 1 and 2 also apply to Figs. 1 and 2). The average of the peak oesophageal eosinophil counts prior to commencing dietary elimination

| Patient No. | 1st endoscopy | 2nd endoscopy | 3rd endoscopy |
|-------------|---------------|---------------|---------------|
| Patient 1   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count (per HPF) | D=60, P=25 | D=20, P=25 | D=3, P=0 |
| Time elapsed (wk) | 0            | 8             | 28           |
| Patient 2   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count | D=37, P=35 | D=20, P=40 | D=8, P=2 |
| Time elapsed (wk) | 0            | 6             | 38           |
| Patient 3   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count | D=43, P=65 | D=35, P=1 | D=14, P=1 |
| Time elapsed (wk) | 0            | 6             | 14           |
| Patient 4   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count | D=15, P=20 | D=4, P=15 | D=1, P=5 |
| Time elapsed (wk) | 0            | 7             | 15           |
| Patient 5   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count | D=10, P=22 | D=16, P=6 | D=1, P=1 |
| Time elapsed (wk) | 0            | 6             | 13           |
| Patient 6   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count | D=30, P=30 | D=20, P=5 | D=0, P=0 |
| Time elapsed (wk) | 0            | 6             | 18           |
| Patient 7   |               |               |               |
| Symptoms    |               |               |               |
| EREFS*      |               |               |               |
| Eosinophil count | D=35, P=5 | D=15, P=3 | D=5, P=0 |
| Time elapsed (wk) | 0            | 7             | 14           |

D, distal esophagus; P, proximal esophagus.
*EREFS is an acronym for a 5-item scoring system of the appearance of the esophagus at endoscopy. The features noted are edema, rings, exudates, furrows, and strictures.
was 38.5 (range, 15–65). Following the initial period of dietary elimination lasting between 6–8 weeks (mean 6 weeks and 4 days) the eosinophil count decreased to an average of 21.5 (range, 15–40). Finally, after an extended period of dietary elimination (mean of 13 additional weeks; range, 7–22 weeks), histological resolution (<15 eosinophils per HPF) was achieved (average peak eosinophil count of 5.2; range, 0–14) in all cases.

The endoscopic appearance (EREFS score) improved significantly between the index endoscopy (mean score, 6.4; range, 5–8) and subsequent endoscopic assessment (mean score, 2.0; range, 1–4; \( p = 0.018, \) Wilcoxon) after the initial period of dietary elimination, and

![Sequential images at endoscopic images demonstrates improvement at 6 weeks (A to B) with corresponding symptomatic resolution despite persistence of esophageal eosinophilia. Images for subject numbers 1–4 are shown. (C) When dietary therapy was allowed to continue, endoscopic appearance remained stable or improved further.](https://apallergy.org)

### Table 2. Characteristics of patients with slow resolution of esophageal eosinophilia with dietary therapy

| Patient No. | Age (yr) | Sex | Previous treatment | Atopic comorbidities | Concomitant medications | Elimination diet |
|-------------|---------|-----|---------------------|----------------------|-------------------------|-----------------|
| 1           | 20's    | Female | PPI | Peanut allergy | Nil | 6 Food* |
| 2           | 60's    | Male | PPI | Seasonal rhinitis, asthma, eczema, valvular heart disease | Losartan, aspirin, salbutamol, budesonide (inhaled) | Milk, egg, gluten, peanut |
| 3           | 20's    | Male | PPI | Seasonal rhinitis, asthma, hypertension, psoriasis | Lisinopril, infliximab, mometasone (inhaled) | Milk, egg, gluten |
| 4           | 20's    | Male | PPI | Seasonal rhinitis | Nil | 6 Food |
| 5           | 40's    | Female | PPI | Nil | Esomeprazole 20 mg daily | 6 Food |
| 6           | 30's    | Male | PPI | Nil | Esomeprazole 40 mg PO twice daily | 6 Food |
| 7           | 30's    | Male | PPI | Asthma, seasonal rhinitis, milk allergy | Esomeprazole 40 mg PO twice daily | 6 Food |

PPI, proton pump inhibitor; PO, per oral.

*6 Food elimination diet compromised initial complete avoidance of wheat and/or gluten, dairy, egg, soy, nuts, and fish/seafood.
remained substantially improved after histologic response was achieved (mean score, 0.6; range, 0–3). All patients described an improvement in symptoms following the initial period of dietary elimination, and this was sustained with extended dietary measures.

**DISCUSSION**

The duration of dietary therapy required prior to endoscopy and determination of response by biopsy and eosinophil count has been empirically set at 6 weeks, and several trials have demonstrated efficacy of between 52%–74% using this length of treatment [2-5, 14]. We herewith present 7 cases where extension of dietary therapy for mean additional 10 weeks (range, 5–22 weeks) resulted in histologic resolution of EoE (<15 eosinophils per HPF) where the shorter 6-week initial treatment course failed using a histologic outcome alone. This presents an alternative approach to current recommendations, and if replicated in a larger patient population, has the potential to alter management algorithms. The unifying features of this cohort includes the improvement in endoscopic appearance and symptoms after the standard 6 weeks of elimination diet, despite persistence of oesophageal eosinophilia traditionally equated with active EoE. This also raises the question of whether a single treatment outcome of EoE, for example a relatively arbitrary eosinophil count threshold, should predominate in terms of management decisions.

The patients described in this case series are typical of larger studies published by our respective centres and elsewhere, with a male predominance and comorbid atopic illness [2, 15]. While chance alone is always presented as an explanation for hitherto novel observations (and remains possible in smaller studies), this well characterised group had biopsies of the upper and lower oesophagus, had progressive reduction of eosinophil count between all sequential endoscopies, and improvement in clinical and endoscopic features that would be in keeping with slow (or incremental) improvement over time. Admittedly, medications that could influence eosinophil count were used to treat asthma in 2 of the patients (inhaled corticosteroids, aspirin), although no change in medication frequency or dose was made throughout the course of dietary therapy, and with these medications one could argue
that any improvement might be limited to the proximal oesophagus. The 2 centres differed slightly in the administration of the elimination diet, the 6 food elimination diet used in Melbourne Australia was more expansive (than that employed in Chapel Hill North Carolina) in that it excluded gluten instead of simply wheat, although it is unlikely that this influenced the slow resolution of eosinophilia discussed, which was nevertheless observed across both groups (and it is as yet unknown if gluten or wheat per se is the trigger for EoE) [2, 11].

In conclusion, we propose that a subset of patients with EoE will benefit from a prolonged period of food elimination before this therapy is declared a failure, and alternative therapies which could include long-term topical corticosteroid use or repeated oesophageal dilatation are utilised. What proportion of patients will benefit, and thus currently are being declared a treatment failure with dietary therapy, is unknown. Given that all the patients described had an initial decline in eosinophil count (albeit not below 15 eosinophils per HPF), improved endoscopic appearance and symptom relief, this triad presents a useful starting point to define a group potentially able to benefit from continued dietary avoidance. Future larger multicentre studies that interrogate pre-existing databases to determine if eosinophil count in fact decreased following dietary elimination (in patients nonetheless classified as nonresponders) may present a clue as to further ‘missed’ cases likely to be similarly helped by extended periods of dietary therapy.

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REFERENCES

1. Philpott H, Nandurkar S, Royce SG, Thien F, Gibson PR. Risk factors for eosinophilic esophagitis. Clin Exp Allergy 2014;44:1012–9. [PUBMED] [CROSSREF]

2. Philpott H, Nandurkar S, Royce SG, Thien F, Gibson PR. A prospective open clinical trial of a proton pump inhibitor, elimination diet and/or budesonide for eosinophilic oesophagitis. Aliment Pharmacol Ther 2016;43:985–93. [PUBMED] [CROSSREF]

3. Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. J Allergy Clin Immunol 2014;134:1093–9.e1. [PUBMED] [CROSSREF]

4. Lucendo AJ, Arias A, González-Cervera J, Yagüe-Compadre JL, Guagnozzi D, Angueira T, Jiménez-Contreras S, González-Castillo S, Rodríguez-Dominguez B, De Rezende LC, Tenias JM. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol 2013;131:797–804. [PUBMED] [CROSSREF]

5. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012;142:1451–9.e1. [PUBMED] [CROSSREF]
6. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. American College of Gastroenterology. ACG clinical guideline: Evidence-based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679-92. 

7. Straumann A, Conus S, Degen L, Frei C, Bussmann C, Beglinger C, Schoepfer A, Simon HU. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:400-9.e1.

8. Molina-Infante J, Rivas MD, Hernandez-Alonso M, Vinagre-Rodríguez G, Mateos-Rodríguez JM, Dueñas-Sadornil C, Perez-Gallardo B, Ferrando-Lamana L, Fernandez-Gonzalez N, Bañares R, Zamorano J. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. Aliment Pharmacol Ther 2014;40:955-65.

9. Lucendo AJ. Meta-analysis-based guidance for dietary management in eosinophilic esophagitis. Curr Gastroenterol Rep 2015;17:464.

10. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003;98:777-82.

11. Reed CC, Safta AM, Qasem S, Angie Almond M, Dellon ES, Jensen ET. Combined and alternating topical steroids and food elimination diet for the treatment of eosinophilic esophagitis. Dig Dis Sci 2018 Jan 29 [Epub]. https://doi.org/10.1007/s10620-018-4931-9.

12. Dellon ES, Cotton CC, Gebhart JH, Higgins LL, Beitia R, Woosley JT, Shaheen NJ. Accuracy of the eosinophilic esophagitis endoscopic reference score in diagnosis and determining response to treatment. Clin Gastroenterol Hepatol 2016;14:31-9.

13. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489-95.

14. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014;146:1639-48.

15. Dellon ES, Speck O, Woodward K, Gebhart JH, Madanick RD, Levinson S, Fritchie KJ, Woosley JT, Shaheen NJ. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol 2015;108:1854-60.