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Title: Multidisciplinary approach to the management of adult eosinophilic oesophagitis in the United Kingdom.

Short running title: management of eosinophilic oesophagitis

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To the Editor,

1. INTRODUCTION

Dietary intervention is effective for the management of eosinophilic oesophagitis (EoE) in both adults and children [1]. The majority of research has been conducted in Spain or the United States [1], with no studies of dietary intervention published in the United Kingdom. Restrictive elimination diets can be challenging and swallowed topical corticosteroids have also been shown to be an effective treatment in adults [2]. Despite their efficacy, disadvantages include risk of candidiasis [3], potential long-term effects such as adrenal suppression [3] and off-label medication use. Proton pump inhibitors (PPIs) are effective for a proportion of patients [4] although with both PPIs and corticosteroids, the underlying triggers of this presumed antigen-mediated condition are not identified and continued use is required to maintain efficacy [3]. A key aspect in the management of any allergic disease is avoidance of relevant allergens.

Through a multi-disciplinary collaboration between Adult Allergy, Gastroenterology and Dietetics, we launched a service to provide dietary intervention for adults with EoE in a UK tertiary referral centre. We recently undertook a retrospective evaluation with the aim to describe the clinical phenotype of EoE in our service and to determine the clinico-pathological response to dietary or medical interventions in this cohort (GSTT service evaluation 6195).

2. METHODS

A search of the histology reporting system was performed in patients who had oesophageal biopsies taken over two years using the term "eosinophil". Patients were also identified by reviewing clinical records. The resulting list was manually screened for eligible patients, namely adults (>16 years) with an oesophageal eosinophil count over 15 per high power field (hpf) and documented history of suggestive symptoms.

In our pathway (Figure 1), all patients with oesophageal eosinophilia were advised to start a PPI as per previous guidelines [5]. Both responsive and non-responsive patients were offered a choice between dietary management, corticosteroids or long-term PPI if responsive. Prior to dietary intervention patients were assessed by both an Allergist and specialist allergy dietitian. They underwent extensive allergy testing using skin prick and serum specific IgE tests and were placed on a test directed exclusion diet if any results were positive (unless solely sensitised to tree nuts). If no target foods were identified through testing, patients were recommended to undergo the six-food elimination diet (SFED), followed by sequential food reintroduction to identify triggers. A further biopsy was taken after six weeks of intervention. If the SFED was not successful, steroids or an elemental diet were recommended.

Eosinophil counts and histological response were compared in those who had both pre and post-treatment endoscopies for PPIs, steroids, and dietary interventions. All were undertaken for a minimum of six weeks for diet and eight weeks for PPI and corticosteroids. Complete histological response was defined as an eosinophil count of less than 5 cells per hpf, with partial response either a count less than 15 per hpf or a reduction of at least 50%. Clinical response was defined as partial (reported improvement but not resolution of symptoms) or complete (asymptomatic). Statistical analysis was

performed using IBM SPSS Statistics Version 23 (2015). Changes in peak eosinophil counts after each treatment were assessed using Wilcoxon signed rank and histological response rates using Fisher exact tests with statistical significance set at $p < 0.05$.

3. RESULTS

We identified 100 patients with a male (n=76/100 [76%]) and Caucasian predominance (n=69/73 [95%]), as shown in Table 1. High levels of sensitisation to both food and aeroallergens were also seen (Table 1). The most common positive foods on allergy testing were: almond (28/57 [49%]), sesame (10/22 [45%]), hazelnut (24/56 [43%]), barley (24/58 [41%]), rye (16/41 [39%]), cow's milk (22/60 [37%]), wheat (23/60 [38%]), and peanut (18/55 [33%]). Test directed elimination diets included exclusion of cow's milk 2/10 (20%); cow's milk and gluten 3/10 (30%); cow's milk, fish and tree nuts 2/10 (20%); cow's milk, soy and tree nuts 1/10 (10%); gluten, oats, soya and foods containing lipid transfer proteins (LTPs) 1/10 (10%); and raw fruits and vegetables 1/10 (10%).

The majority (n=17/23, 74%) in the PPI group were prescribed 40mg omeprazole. Others were prescribed: 20mg omeprazole 1/23 (4%), 30mg lansoprazole 2/23 (9%), 40mg pantoprazole 1/23 (4%), unknown PPI 2/23 (9%). In the steroid group 11/12 (92%) were prescribed fluticasone via metered dose inhaler (250mcg, n=1; 500mcg, n=5; 750mcg, n=2; 1000mcg, n=1; 2000mcg, n=1; unknown dose, n=1) and 1/12 (8%) was prescribed oral viscous budesonide (2mg). This was given using an inhalation suspension mixed with amino acid formula.

Outcomes from different interventions are shown in Figure 2. There were no significant differences between groups in terms of age, gender, atopy, disease duration or clinical features. There was a non-significant trend towards increased response in dietary versus pharmacological management. The decrease in median [IQR] peak eosinophil count was significant for allergy test-directed (62[38] vs 23 [29]; n=10; P=0.036) and SFED (47[46] vs 10 [46]; n= 20; P=0.006), but not for any other intervention. Histological response (complete or partial) was seen in 35% for PPI (n=23), 50% corticosteroids (n=12), 65%

SFED (n=20), and 50% allergy- test directed diets (n=10). Elemental diet induced remission for both patients who underwent this intervention. Success was lower (17%) for 'other elimination diets' (n=6), which most commonly included empirical elimination of dairy and wheat. For all treatments, clinical response rates were higher than histological rates, particularly for dietary interventions: 52% PPI, 58% steroids, 75% SFED, 90% test-directed, 83% other elimination diets, and 100% elemental.

In 14 patients dietary triggers were identified following food reintroduction and these were confirmed by either repeat biopsies (n=12) and/or a clear cut return of symptoms (n=3). Ten patients completed the reintroduction process, and 5/10 (50%) had a single confirmed trigger, 3/10 (30%) two confirmed triggers, 2/10 (20%) three or more confirmed triggers. Dairy was the most common trigger (8/14 [57%]), following by gluten containing cereals (4/14 [29%]), egg (2/14 [14%]) and (1/14 [7%]) for each of the following: soy, nuts, crustaceans and raw fruit.

Weight loss was common in patients undergoing dietary intervention, with 15/23 (65%) experiencing some degree of weight loss and for 4/23 (17%) this was clinically significant (>10%). The median pre-diet BMI was 22.8 kg.m⁻² (interquartile range 5.0 kg.m⁻²) and 14/37 (38%) were overweight (BMI> 25 kg.m⁻²).

4. DISCUSSION

This retrospective study is the first to describe and report outcomes for dietary and medical management of adult EoE in a real life UK clinical setting. Our cohort had similar characteristics previously described with a high proportion of males, Caucasians and high incidence of atopy. We found a non-significant trend towards better outcomes in dietary compared to medical interventions. Response rates for dietary management mirror the results of previous studies [1]. Lower response rate to steroids may be due to the small sample size or due to inadequate dosages, as well as potential poor adherence. We found lower response rates to PPIs compared to other studies [4], which may also be due to poor adherence or inadequate dosing, as only 74% were known to be prescribed the recommended amount. Of note, only half of our overall cohort had a follow up endoscopy on treatment and therefore results may be biased if patients responded symptomatically to a PPI or steroids and elected not to undergo a further endoscopy. An allergy-test directed approach has previously been found to be less effective than other dietary approaches, although we saw a higher success rate compared to other adult studies [1]. This may be due to the small sample size or use of fresh foods for skin prick testing, which warrants further investigation. However, even with a lower chance of remission a potential advantage of an allergy-test directed diet over other interventions is a less restrictive diet if successful, as in our cohort the majority (8/10) were avoiding three foods or less. A four-food elimination diet is another possible approach, although there is a lesser established base of evidence compared to other interventions.

A recent large multicentre trial in Spain found that a “step-up” approach from two food elimination (milk and wheat) to four (adding egg and legumes) then six (adding fish and tree nuts) overall saved time and reduced endoscopies [6]. Given that our cohort had

similar incidences of common food triggers, this may also be an effective approach in our population.

Our higher rates of clinical compared to histological response may be explained in part by missing data and lack of a validated tool to measure symptom response, instead relying on subjective reporting. It has been shown that symptoms often do not correlate with oesophageal biopsy results [7] and recent European guidelines recommend histology as the mainstay for diagnosis and monitoring [3]. Repeated endoscopies do place an additional burden on both the patient and the health service, but reliance on symptom improvement may mask persistent eosinophilia, which in the long-term may lead to oesophageal remodelling and stricture formation [8]. It appears that over time EoE in adults progresses from an inflammatory to a fibro-stenotic condition [4], this being potentially harder to treat.

An important question remains regarding long-term efficacy of elimination diets for EoE. One recent study found that in patients who were able to adhere, dietary elimination remained effective, but over half of patients relapsed due to compliance or iatrogenic food reintroduction [9]. As more patients are being treated with dietary intervention, further evidence regarding long-term outcomes is awaited.

Although weight loss was common, many patients were overweight and therefore for some weight loss may have been intentional or desirable. Nevertheless, the restrictive nature of dietary intervention and impact on nutritional status highlights the importance of support from a dietitian. The recent AAAAI Workgroup report recommends when to refer and offers online resources to support those who may not have access to a dietitian [10].

Limitations include the retrospective design and small sample size in different treatment arms, which likely accounts at least in part for the lack of significant differences between groups. Samples undergoing different interventions were not randomised or matched which introduces a source of potential bias. Additionally there were missing data, in particular half of the cohort did not have a follow-up endoscopy on treatment.

In conclusion, we have shown that dietary management of adult EoE can be effective in a real life UK setting using a multi-disciplinary approach including a specialist dietitian. Less-restrictive initial approaches such as test-directed or step-up protocols may be preferable, even if efficacy is lower. Further research would be beneficial to determine how to predict response to treatment as well as focussing on long-term outcomes.

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Legends to figures

Figure 1

Sequence of treatment strategies following diagnosis of EoE. Following a PPI trial, patients were offered a choice between diet or corticosteroids. Dashed lines indicate subsequent treatment following non-response. *PPI-responsive patients were also offered treatment with diet or corticosteroids.

Figure 2

Histological and clinical response rates to different treatments. Complete histological response is defined as eosinophil count < 5 cells/hpf and partial either 5-15/hpf or >50% reduction in eosinophil count. A complete clinical response was absence of symptoms whereas a partial clinical response was improvement but not resolution of symptoms.

PPI: proton pump inhibitor, SFED: six food elimination diet, TDED: test directed elimination diet, OED: other elimination diet, ED: elemental diet

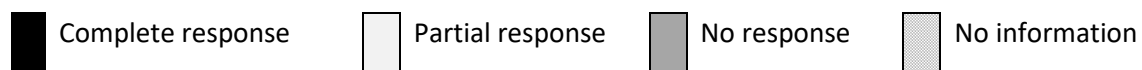
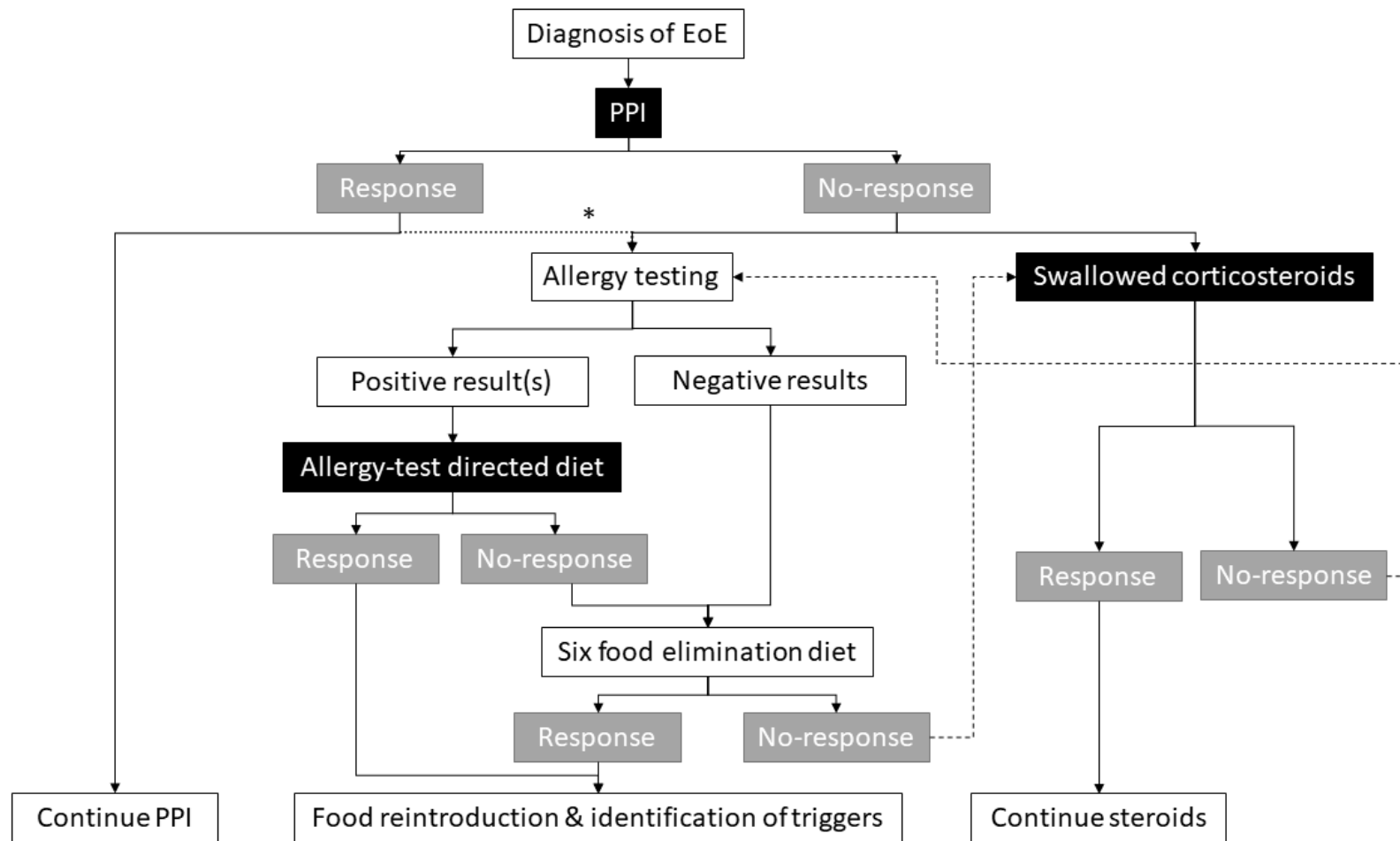
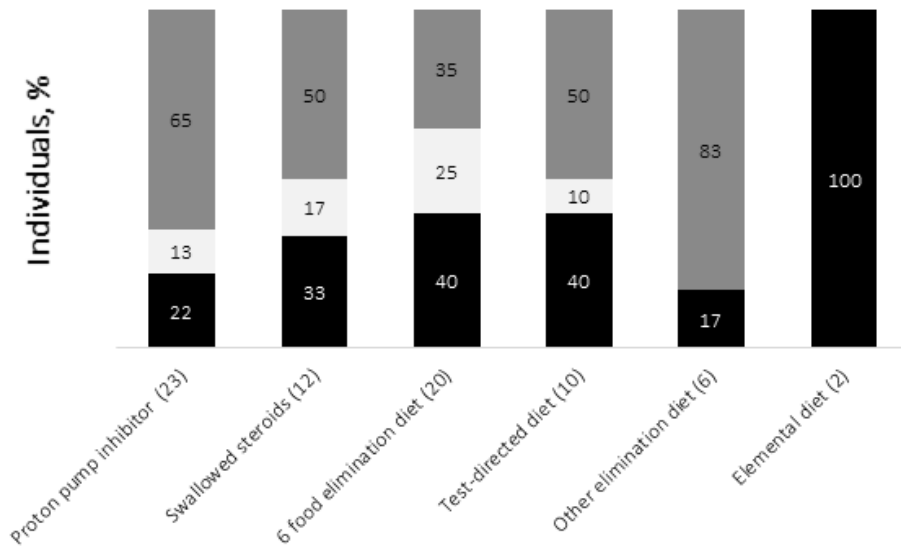
 Complete response Partial response No response No information

Table 1: Patient characteristics

Demographics	(n=100)	
Age (median [IQR])	35 [11]	
Male (n/N (%))	76/100	(76)
Ethnicity (n/N (%))		
Caucasian	69/73	(95)
Black/ mixed black	4/73	(5)
Atopic conditions (n/N (%))		
Any	65/87	(75)
Rhinitis	47/87	(54)
Asthma	33/87	(38)
Eczema	17/87	(20)
Food allergy	24/87	(28)
Positive allergy tests (n/N (%))		
Any food or aeroallergen	52/63	(83)
Aeroallergen	36/52	(69)
Food	46/62	(74)
Food- SPT only	38/59	(64)
Food- IgE only	35/60	(58)
Symptoms at baseline (n/N (%))		
Dysphagia	83/91	(91)
Self-limiting food retention	68/85	(80)
Food impaction	38/79	(48)
Heartburn or reflux	42/88	(48)
Regurgitation or vomiting	31/87	(36)
Chest pain	15/85	(18)
Endoscopic features at diagnosis (n/N (%))		
Trachealisation	50/94	(53)
Furrows	38/94	(40)
Stricture	20/94	(21)
Exudates	16/94	(17)



Histological Response



Clinical response

