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NARRATIVE REVIEWS

Disease Burden and Spectrum of Symptoms that Impact Quality of Life in Pediatric Patients with Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a progressive type 2 inflammatory disease characterized by symptoms related to esophageal dysfunction and significant esophageal eosinophilic infiltration. It can affect patients from infancy through adulthood. Pediatric EoE has a multidimensional impact on the quality of life of both patients and their families. Nonspecific symptoms mimicking other gastrointestinal conditions, such as food refusal, failure to thrive, and feeding difficulties, may profoundly affect young children's eating skills, growth, and psychosocial status, as well as impact family financial conditions. In adolescence, dysphagia and esophageal food impactions often lead to feeding-related anxiety and influence social lives. Delays in diagnosis, arising from lack of awareness among families and clinicians and compensatory eating behaviors, could increase the risk of fibrostenotic complications, which may ultimately add to the symptom burden. Currently available treatment options include proton pump inhibitors, dietary therapies, swallowed topical steroids, esophageal dilation, and biologic therapy. Despite the efficacy of these approaches, disease burden may be further impacted by their limitations, including poor adherence rates, refractory disease, potential long-term safety concerns, and high costs for care. Thus, there is a need for more timely diagnosis in clinical practice and novel targeted disease-modifying therapies better tailored to treat various phenotypes of EoE, aimed at reducing the physical and psychosocial burdens on patients and their caregivers.

Keywords: Eosinophilic Esophagitis; Disease Burden; Dupilumab; Pediatric; Quality of Life

Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease characterized by symptoms related to esophageal dysfunction and esophageal eosinophilic inflammation.[1,2] Concomitant atopic conditions, including asthma, allergic rhinitis, food allergy, and atopic dermatitis, are commonly associated with EoE, irrespective of age.[3] EoE affects patients from infancy through late adulthood.[4,5] Since the early 2000s, the prevalence of EoE has been steadily increasing globally, with the estimated EoE prevalence of 42.2/100,000 and 34.4/100,000 inhabitants for adults (≥18 years old) and children (<16 years old), respectively, based on population-based studies conducted in the USA, Canada, and Europe, with some representation of South America and Western Australia.[6] In children, a stable incidence of EoE has been reported over time.[6]

The natural history of EoE has been evaluated in many retrospective studies in adult and pediatric patients.[1] EoE can gradually progress from an inflammatory phenotype to a more fibrostenotic phenotype.[1,2] A longer duration of untreated EoE caused by diagnostic delays and gaps in care[7,8] increases the likelihood of fibrostenotic complications, which result in dysphagia and food impaction.[9,10] Younger patients with EoE tend to present an inflammatory phenotype with other comorbid atopic conditions and food allergies,[11] whereas older patients are more likely to present fibrostenotic complications.[3,7] In a retrospective study of patients with EoE, the odds of a fibrostenotic

Abbreviations used in this paper: 4-FED, 4-food elimination diet; 6-FED, 6-food elimination diet; AA, amino acid; AS, adrenal suppression; BID, twice daily; BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos, eosinophils; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; FDA, Food and Drug Administration; FTT, failure to thrive; GERD, gastroesophageal reflux disease; HS, hora somni; IL, interleukin; MOA, mechanism of action; PPI, proton pump inhibitor; QOL, quality of life; qw, once a week; R, receptor; RCT, randomized controlled trial; STC, swallowed topical corticosteroid; TSLP, thymic stromal lymphopoietin.

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phenotype doubled for every 10-year increase in age, indicating possible disease progression from chronic inflammation to esophageal remodeling and fibrostenosis.[11] The pattern and rate of EoE progression, however, may vary, and fibrostenosis has been reported in untreated children.[12]

Infants and young children with EoE often have abdominal pain, gastroesophageal reflux/vomiting, and a wide range of feeding difficulties, whereas adolescents and teenagers commonly have chronic dysphagia and intermittent esophageal food impaction.[2,4,13–16] While these symptoms can be nonspecific, they can impact their quality of life (QOL).[17] The chronic symptoms of EoE may affect overall psychosocial aspects of life in the domains of feeding behaviors, sleep, social, school, and emotional functioning.[17] Concurrently, their caregivers may also have elevated anxiety levels and stress related to their child's well-being, and increased financial burden due to the long-term health-care costs.[18,19] As such, further studies are warranted to better understand the disease burden.

Currently available therapies for pediatric EoE include food elimination diets, off-label use of proton pump inhibitors (PPIs), swallowed topical corticosteroids (STCs), esophageal dilation, and, more recently, biologics.[5,20–24] Despite the effectiveness of pharmacologic and dietary interventions, up to approximately 40% of pediatric patients who received either dietary interventions or STCs have been shown to experience failure in achieving histologic remission.[25] Furthermore, the potential long-term adverse effects of the pharmacologic and dietary therapies in children are not clear and remain areas of investigation. The biologic dupilumab is indicated for patients aged $\geq$ 1 year, weighing $\geq$ 15 kg, in the USA,[26] and for patients aged $\geq$ 12 years, weighing $\geq$ 40 kg, in Europe.[27] Dupilumab may be considered by clinicians after taking into account individual patient preferences, as well as access to the drug.[23] Several clinical studies are underway assessing the use of STCs and biologics for pediatric EoE, including APT-1011,[28] budesonide oral suspension (BOS),[29] cendakimab,[30] and tezepelumab.[31]

The objectives of this review are to describe the psychosocial and QOL burdens of EoE in children ($\leq$12 years; preschool-aged and school-aged), adolescents (13–18 years old), and their caregivers, and to highlight how challenges in the diagnosis and treatment of the disease particularly affect the pediatric population.

Clinical Presentation of Pediatric EoE

Differential Spectrum of EoE Symptoms in Children and Adolescents

Young children with active EoE often have nonspecific symptoms compared with the majority of adolescents and/or adults.[4,32,33] Preschool-aged children may even have fewer specific symptoms and are unable to clearly verbalize those symptoms. Feeding difficulties, which can occur due to multiple etiologies, are common, as are persistent gastroesophageal reflux and vomiting.[4,34] EoE-related symptoms tend to evolve from vague complaints, such as food refusal and abdominal pain in young children, to more obvious and slightly more specific symptoms, such as chest pain, dysphagia, and food impaction in adolescents and adults.[4,32–34] In adolescents, EoE may be misdiagnosed as eating disorders, because symptoms such as food-related anxiety, vomiting, and food aversion are shared by both conditions.[34] Detailed clinical symptoms of EoE based on age are described in Figure 1.[4,32–35]

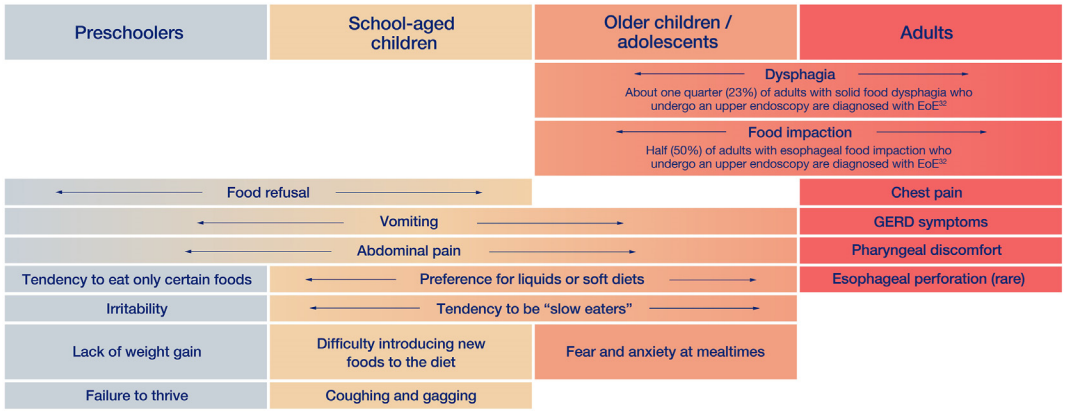

Figure 1. Spectrum of EoE symptoms among different age groups. EoE symptoms vary between age groups. In preschoolers, food refusal, along with a tendency to eat only certain foods, irritability, vomiting, and abdominal pain, lead to FTT and lack of weight gain. In school-aged children, food refusal, difficulties in introducing new foods to the diet, preference for liquids and soft diets, and a tendency to be "slow eaters" are common symptoms. The most frequent gastrointestinal symptoms include abdominal pain and vomiting in this age group. Adolescents with symptoms of dysphagia and food impaction also maintain a preference for fluid intake or soft diets, tend to be "slow eaters," and show fear and anxiety at mealtimes. In adults, dysphagia and food impaction are common symptoms, along with chest pain, GERD symptoms, nonspecific pharyngeal discomfort, and, rarely, spontaneous esophageal perforation.[16,32,33] GERD, gastroesophageal reflux disease.

Challenges in Diagnosing EoE in Children and Adolescents

Diagnosis of EoE, the components of which are similar at all ages, requires a comprehensive evaluation of clinical symptoms and assessment of esophageal biopsies, with supportive findings from endoscopy.[5,36] The minimal histologic findings necessary for a diagnosis of EoE in the appropriate clinical setting are increased eosinophil (eos) counts ($\geq$15 eos/high-power field or 60 eos/mm^2).[35,36]

Time from initial symptom presentation to diagnosis varies across different age groups. A retrospective analysis of the Swiss EoE database established in 1989 showed that diagnostic delay was longest in the young patient population ($\leq$20 years old) and decreased with increasing age.[7] The results from this study, however, need to be interpreted with caution in the context of pediatric EoE because the analysis included both adult and pediatric patients together. Based on the European Pediatric EoE Registry analysis (2015–2017; patients $\leq$ 18 years old), the diagnostic delay was longer in children $\leq$ 10 years old (2.1 years) compared with children $>$ 10 years old (1.3 years; $P = .01$).[37] However, a study conducted in the USA demonstrated different results regarding the duration of diagnostic delay among pediatric patients.[3] According to a registry established by the Consortium for Food Allergy Research (2011–2016; patients 6 months–65 years old), the interval between symptoms and diagnosis was shorter in younger children than in older children, with median diagnostic delay of 2 years in patients 11–17 years old and 1 year in children $<$ 11 year old.[3] Furthermore, a systematic analysis using studies conducted in North America and Europe (1974–2017) reported that the average diagnostic delay was 1.2–3.5 years in children (5.9–12.0 years old), 3.0–8.0 years in adults (29–30 years old), and 2.5–6.8 years in populations that include both children and adults.[38] Thus, the time of diagnostic delay in EoE is approximately 1–4 years in pediatric EoE.

Potential reasons for delayed EoE diagnosis include nonspecificity of presenting symptoms,[39] compensatory eating behaviors leading to a delay in seeking medical attention,[3,39] the need to perform an esophageal biopsy to confirm diagnosis,[39] and hesitation from the patient, family, or clinicians to perform the needed endoscopy.[7,39] In young children with EoE, delayed diagnostic time was significantly associated with failure to thrive (FTT) and feeding problems.[40] Furthermore, unawareness of the disease both in patients and the medical community may add to delays in diagnosis or early misdiagnosis of symptoms.[39]

Delayed diagnosis of EoE is associated with an increased risk of esophageal stricture formation in a time-dependent manner in adults.[7] It is important to note that esophageal narrowing can be seen in the pediatric population,[11] which may in large part be inflammatory.[41] The observed phenotype may have an inherently different pathophysiology than the eventual outcome of EoE—namely fibrostenotic phenotype. Although Ruffner and Spergel described that the risk of stricture formation in the pediatric population may be less pronounced than in the adult population,[42] a decreased esophageal distensibility with lamina propria fibrosis and fibrotic phenotype have been observed in pediatric patients (3–18 years old) with EoE more frequently than in control patients without EoE who had normal upper endoscopy and biopsies.[43] These findings suggest that some children with EoE are at high risk of developing stenosis and fibrotic strictures if left untreated for a long period of time.

In children with EoE, a short course of systemic steroids has been shown to reverse moderate-to-severe stricture,[41] and, similarly, topical steroid treatment or dietary restriction for as short as 3 months has led to resolution of lamina propria fibrosis.[44] Thus, timely diagnosis and institution of successful therapy at an early stage may be particularly important to prevent potential progression to fibrostenosis in pediatric patients with EoE.

Impact of Pediatric EoE on Feeding Behaviors, Child Growth, and Psychosocial Functioning in Children and Their Caregivers

EoE may have a substantial impact on the QOL of pediatric patients and their families (Figure 2).[13,14,17,18,45–47] In young children (1–7 years old) with EoE, in whom nonspecific symptoms such as abdominal pain, nausea/vomiting, and diarrhea are common, abnormal feeding behaviors are quite frequent, as measured by the Behavioral Pediatric Feeding Assessment Scale.[13] Wu et al also reported that children (2.5–18 years old) with eosinophilic gastrointestinal disorder (85% EoE, 15% eosinophilic gastroenteritis) had greater childhood behavioral problems associated with feeding and more parental maladaptive emotions related to child feeding compared with healthy children.[14] Of note, younger children (2–7 years old) were found to have more frequent behavioral problems related to feeding than older children (8–12 years old).[14] In addition to the adverse impact caused by EoE symptoms, overly restricted dietary elimination therapies during critical phases of feeding development can limit patient exposure to a wide range of textures and flavors of food from infancy to adolescence.[15,16] A small case series in the USA reported that EoE and its symptoms disrupted the development of oral motor and sensory skills, as well as family dynamics during mealtimes, which ultimately required management with multidisciplinary medical support from allergists, gastroenterologists, dieticians, and occupational therapists.[15]

About 10%–24% of young children with EoE present with FTT.[48–50] In particular, a retrospective chart review of 62 Canadian children with EoE showed that 24% (n = 15/62) had FTT based on anthropometric criteria at diagnosis.[48] Although the majority of the patients resolved their FTT at a median of 18 months after diagnosis with medical interventions such as elimination or elemental diets, STCs, or

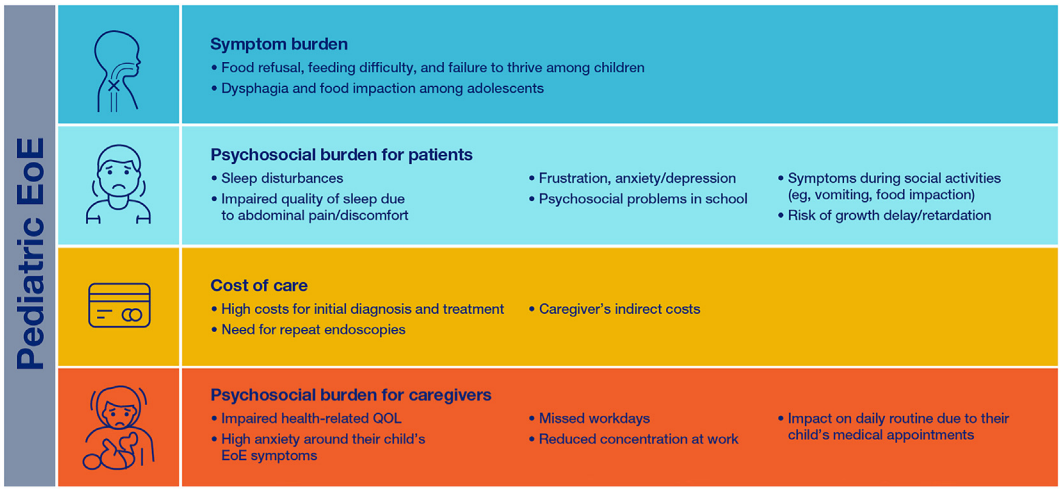

Figure 2. Pediatric EoE is associated with clinical, psychosocial, and financial burdens. Pediatric EoE has a multidimensional impact on the QOL of both patients and their caregivers. The chronic, progressive nature of EoE results in significant clinical, psychosocial, and financial burdens.

oral prednisone, 6 children had unresolved FTT despite treatment.[48] Overall, timely recognition of FTT may help to identify the disease at an earlier stage, which may prevent complications of FTT such as nutritional deficiencies and faltering in normal growth arising from feeding difficulties.[16]

In a retrospective cohort of 64 children with EoE, 69% had some form of psychosocial difficulty, including social problems, anxiety, sleep difficulties, depression, and problems in school.[17] In young children (0–4 years old), sleep disturbances and feeding problems were more common than in older children or adolescents (5–18 years old), which could potentially affect their caregivers' QOL as well.[17] Regardless of children's age, feeding/appetite problems were significantly associated with more sleep problems and social difficulties.[17] Because children tend to spend a significant amount of time on eating with family, friends, and schoolmates, difficulties associated with meals in EoE, such as prolonged mealtimes, food limitations/avoidances, and maneuvers to overcome dysphagia or food impaction, may affect overall psychosocial function by interfering with children's motivation or comfort with peer interactions, family, and sports activities.[17]

In older children who had pain or discomfort, more sleep problems as well as social and school functional difficulties were found relative to those without pain/discomfort.[17] Furthermore, children (4–12 years old) with EoE who reported persistent epigastric pain had greater sleep disturbance, lower sleep efficiency, and more frequent wake events after sleep onset than those without epigastric pain.[47] With regards to emotional functioning, depression or anxiety were more predominant in older children (11–17 years old) compared with children aged $<$ 11 years.[3] Anxiety symptoms appear to arise from concerns about chronic symptoms, fear of choking on food, long-term dietary restriction therapies, gastric tubes, and recurrent endoscopies.[46,51]

Caregivers of pediatric patients also have impaired QOL. A prospective study of 97 pediatric patients showed that caregivers' QOL was reduced by the severity of their child's EoE symptoms, as assessed by the Pediatric Quality of Life Inventory Family Impact Module.[19] The majority of pediatric EoE caregivers report that their work concentration and daily routine are impacted by their child's EoE, including taking time away for medical appointments and hospital stays.[18] Furthermore, more than half of caregivers had reduced health-related QOL since their child's EoE diagnosis, as measured by the Bakas Caregiving Outcome Scale.[18] Caregivers of young children aged 13–23 months had poorer QOL compared with caregivers of children aged $>$ 13 years, indicating that younger age of patients has a greater impact on the health-related QOL of caregivers.[18]

Overall, the chronic symptom burden of food refusal, poor appetite, and pain or discomfort could affect age-appropriate eating skills, child growth, and the overall QOL of patients and their caregivers.

Burden of Care in Pediatric EoE

Cost of Care in EoE

Regardless of age, patients with EoE have significantly higher cost of care than those without EoE in the USA. According to a matched, case-control analysis using a US Health Plan Claims Database (2009–2010; patients aged 0–64 years), the estimated annual health-care cost for patients with EoE was $1.4 billion,[52] although the cost of care in other countries is less well characterized. Stratification by age ($<$18 vs 18–64 years) indicated that health-care utilization costs during the study period were approximately 20% higher in children (mean cost $15,956) than in adults (mean cost $12,734).[52] In a single-center retrospective study, the initial cost of diagnosis—defined as hospital

charges and physician fees—for each patient was estimated at $18,808 in pediatric patients. The first-year costs for EoE disease management were $20,691 for steroid therapy, $60,643 for elemental diets, $80,485 for 6-food elimination diets (6-FEDs), $55,864 for 4-food elimination diets, and $17,772 for milk elimination diets.[53]

Although EoE is primarily managed in the outpatient setting, the hospitalization rate increased by nearly 70% from 2010 to 2016 based on a cross-sectional analysis using the US National Inpatient Sample, with the total annual cost for EoE-related admissions being $24 million in children and adults.[54] Irrespective of age, hospitalization charges were higher for EoE cases with complications (stricture/spontaneous rupture/perforation/laceration of esophagus or esophageal hemorrhage), with such patients being charged 130% more than minor cases with no complications.[54] A unit increase in the hospitalization severity significantly increased the costs by an average of $6784 for extremely severe conditions with complications and $1673 for moderate conditions.[54] The most common procedure performed on inpatients with a diagnosis of EoE was esophagogastroduodenoscopy (EGD) with biopsy, with the mean cost for each inpatient EGD being $4483.[54] While the costs for care are generally high on a per-patient basis across pediatric and adult patients, inpatient claims in EoE are relatively uncommon.[55]

Families and caregivers of pediatric patients with EoE also face financial burdens (Figure 2). Costs of care in both inpatient and outpatient settings are significantly higher for pediatric patients compared with adult patients, with the median cost per EoE case being $4001 for pediatric patients vs $1906 for adult patients.[56] Furthermore, caregivers of children and adolescents with EoE have estimated annual indirect costs of $2473 and $16,487 due to reduced working hours and stopping work, respectively.[57]

Overall, pediatric patients with EoE and their caregivers in the USA face increased all-health-care costs due to medications, special diets, and multiple endoscopies, and they experience a significant impact on their daily lives, contributing to burden of care. Of note, the costs of care were analyzed before the approval of biologic dupilumab for EoE in 2022. On the other hand, evidence on the direct and indirect financial burden to patients with EoE and their caregivers from countries outside the USA is scarce; 1 Australian survey study reported an annual mean health-care–related out-of-pocket expenditure cost of AUD $3064 per child with EoE.[18] It is important to note that many of the aforementioned costs are likely to be lower in many Organisation for Economic Co-operation and Development countries than in the USA because of the lower estimated health-care costs and/or the availability of government health insurance coverage.[58,59] As such, it is plausible that direct health-care costs for EoE may be lower in other countries, but future comparative studies are necessary to further elucidate the global financial burden of pediatric EoE.

Current Status of EoE-Specific Transition of Care from Adolescence to Adulthood

As a component of burden of care, there remain challenges and unmet needs in the transition of care in pediatric EoE. Given the chronic nature of type 2 inflammation in EoE, management of EoE requires continued coordination of care from childhood to adulthood. Specific barriers to effective health-care transition for patients with EoE include a knowledge gap in patient/parent experience related to health-care transition, disjointed communication between pediatric and adult health-care professionals, and lack of a standardized health-care transition system.[60–63]

In an online survey of patients aged $\geq$ 13 years with EoE/eosinophilic gastroenteritis and the parents of those patients, 78% of patients and 76% of parents reported having no prior knowledge of the health-care transition process.[62] Additionally, patients with EoE struggled with meal planning, food shopping, and cooking/finding foods, and had limited knowledge of their insurance coverage during the transition of care from adolescence to adulthood, based on another survey.[60] In the survey, most patients reported having confidence in their knowledge of managing their EoE, but nearly 50% of patients worried about managing their condition in the future.[60]

In general, previously published EoE-specific health-care transition models suggest initiating a transition-of-care program from early adolescence (13–15 years old) to late adolescence/young adults ($\geq$18 years old), including education on disease course, medications, insurance, responsibilities of care (eg, scheduling appointments for patients/parents), and joint review of medical records for pediatric and adult providers.[61,63] For effective transfer of medical care, facilitating multidisciplinary collaboration among allergists, gastroenterologists, pediatricians, dieticians, psychologists, and social workers has also been recommended to improve continuity of care through a shared decision-making process.[63] Despite the proposed models for an EoE-specific health-care transition program, there is no standardized transition system for both patients and providers,[61] which is an area of this chronic disease that needs further improvement.

Treatment Options and Limitations for the Management of Pediatric EoE

Currently available treatment options include dietary therapy (elemental, test-directed elimination, and empiric elimination diets), PPIs, and STCs (fluticasone, budesonide) in pediatric patients. The biologic dupilumab is available for patients as young as 1 year old in the USA and for patients $\geq$ 12 years old in Europe.[23,26,27] When strictures are present in pediatric patients, 22%–31% of cases undergo esophageal dilations to relieve symptoms of dysphagia.[64,65]

Dietary Therapies

Because food antigens are implicated in the development of EoE, diet modification is a therapeutic approach that targets the cause of the disease regardless of age.[5] Dietary therapies for EoE include an elemental diet, a food allergy test-directed elimination diet (based on results of skin prick tests and atopy patch tests), and an empiric food elimination diet.[5,66]

Elemental diets, in which all foods are removed from the diet except for a liquid formulation of free amino acids (AAs) fortified with nutrients, are associated with a 90.8% histologic remission rate and are shown to be effective in reducing symptoms in children and adolescents.[5,67,68] However, certain limitations to this dietary therapeutic approach exist, especially in young children with EoE who have food aversion. The poor taste of the AA-based formula makes it unpalatable, which may lead to requiring tube feeding.[66] Large volumes of the AA-based formula may also need to be provided to young children to meet their caloric needs for normal growth, which they often cannot manage orally, again leading to tube feeding.[66] Furthermore, because feeding skills are acquired through the presentation of foods during the first 3 years of life, an elemental diet could delay normal development of oral sensory and motor skills in young children.[66,69] In adolescents, an inability to eat solid foods, particularly in social situations, may significantly affect their QOL.[5,46]

Empiric elimination diets, currently the most common and effective dietary therapy, consist of avoiding the most common food allergens known to trigger EoE, including milk, wheat, eggs, soy, fish/shellfish, and peanuts/tree nuts, without any allergy testing.[66] In a systematic review and meta-analysis, the histologic EoE remission rate using the 6-FED was estimated at 72.8% in children, which was higher than the histologic remission rate achieved with test-directed food elimination (47.9%).[67] Less restrictive empiric elimination diets, including the 4-food elimination diet (milk, wheat, eggs, soy) and the milk elimination diet, have also shown to be effective, with histologic remission rates reported as high as 60.0% and 66.3%, respectively.[67] Empiric elimination diets may be preferred by patients and families over elemental diets, with the advantages of lower costs, improved adherence, and the need for fewer endoscopies.[67]

Although dietary therapies are effective in children, they can lead to nutritional inadequacy when provided to patients with underlying feeding difficulties and without appropriate guidance from physicians or dietitians.[66,69] Regular EGDs with esophageal biopsies for histologic follow-ups on EoE disease activity following food reintroductions add to patient burden,[66] and repeated exposure to the anesthesia used to perform the EGDs may have an impact on the developing brains of young children.[70] For some patients and caregivers, restricted insurance coverage for the high-cost AA-based formula has been shown to be a barrier to affordable access.[66,71] Furthermore, the costs of food shopping for empiric elimination diets may add to patient/caregiver burden, because the average weekly cost of shopping at a standard grocery store is higher, costing $92.54 for a 6-FED vs $79.84 for an unrestricted diet ($P = .0001$) in the USA. Additionally, a patient shopping at a standard grocery store for the 6-FED needs a higher proportion of items from a second store to complete the shopping compared with a patient consuming an unrestricted diet (32% vs 3%, $P = .0001$).[72]

Overall, children with EoE undergoing highly restrictive diet therapies without adequate supervision and support may have delayed sensory oral and motor development, and result in inadequate nutrition and feeding difficulties. Furthermore, patients and caregivers may have to carry the additional spending associated with dietary therapies (Table 1).[5,66,69,71,72]

PPIs

Although there are currently no approved PPIs for the treatment of EoE, PPIs are considered a low-cost first-line treatment in pediatric patients, and dosing recommendations for PPI therapy have been derived from clinical guidelines based on experts' clinical experience.[5,32]

PPI therapy leads to clinical response in up to 65% and histologic remission in up to 54% of pediatric patients with EoE, and is generally considered tolerable and safe.[5,73] Despite the effectiveness of PPIs, some children with EoE do not respond to a high PPI dose, or lose response to PPIs within 1 to 2 years after achieving histologic response.[95–97] Furthermore, patients receiving PPIs may need to remain on a high dose after achieving histologic remission, because approximately 30% of patients who achieved histologic remission on esomeprazole showed histologic relapse after receiving a reduced maintenance dose.[98]

In addition to disease relapse, early use of PPIs may have long-term adverse impacts on young children.[80,99–101] With an increase in the general use of PPIs in infants worldwide,[102,103] there are concerns about the potential negative effect of PPIs on the microbiomes of the pediatric population.[101] In a prospective, longitudinal study, early use of PPIs in infants with gastroesophageal reflux disease has been shown to disrupt the intestinal microbiome, with a decrease in *Lactobacilli* and *Stenotrophomonae* and an increase in *Haemophili* following PPI treatment for a mean period of 18 weeks.[80] Additionally, use of PPIs in the context of asthma is thought to cause interference in the balance between the symbiotic and pathologic species in the intestinal and respiratory tract.[104] Of note, the long-term effects of PPI use in children with EoE have not been explored thus far; however, a previous study in early infancy suggests that PPIs may increase the risk of a food allergy.[100] Although intestinal permeability may be increased in early infancy compared with later in childhood, another report in adults found elevated levels of food-specific immunoglobulin E with PPI use.[105]

Overall, current literature suggests that pediatric patients with EoE may relapse while on PPI treatment or if not

Table 1. Current Therapeutic Options and Limitations for EoE in the Pediatric Population

	Dietary therapies	PPIs	STCs	Esophageal dilation	Dupilumab
Efficacy in histologic endpoint	Histologic remission rate • Elemental diet: 90.4% • 6-FED: 72.8% • 4-FED: 60.0% • Milk elimination diet: 66.3% • All based on a systematic review and meta-analysis[67]	Histologic remission rate • 54.1% based on a systematic review and meta-analysis[73]	Histologic response rate[a] • Budesonide oral suspension (2 mg BID): 53.1% of patients aged ≥ 11 y (vs 1% in placebo) in Study 1 and 38.0% (vs 2.4% in placebo) in Study 2 following 12 weeks of treatment[24] • Off-label use of STCs: 64.0%–87.0% based on RCTs and retrospective studies[74–76]	No influence on histologic endpoint • Sustained symptom relief in 95% of patients of all ages undergoing dilation[77]	Histologic remission rate (based on the phase 3 EoE TREET and KIDS studies[78,79]) • At wk 52, 85.0% of patients aged ≥ 12 y who received dupilumab at a dose of 300 mg qw since baseline and 68.0% of those who received placebo from baseline until wk 24 and switched to dupilumab 300 mg qw[78] • At wk 16, 68.0% of children aged 1–11 y who received higher-exposure dupilumab[b] and 58% of children on lower-dose dupilumab[b]; the remission rate was generally sustained through wk 52[79]
Adverse events and potential long-term adverse impact	• Delay in sensory oral and motor development[5,66] • Nutrition inadequacy[66] • Impairment in feeding skills[69] • High cost of elemental diet and increased cost of groceries associated with 6-FED[66,71,72]	• Disruption of microbiome in the gut in infants[80]	• Respiratory tract infection[24] • Oral and esophageal candidiasis[24,81–86] • Headache[24] • Gastroenteritis[24] • Throat irritation[24] • Erosive esophagitis[24] • Risk of AS[24,87–89] • High cost of off-label STCs[90–92]	• Postprocedural chest pain[93] • High cost of endoscopy and anesthesia for dilation[94]	• Injection-site reaction[26,78,79] • Upper respiratory tract infections[26] • Arthralgia[26] • Herpes viral infections[26] • Helminth infection (in EoE KIDS part B) [26] • Lack of efficacy and safety data beyond 1 year • High cost of dupilumab

4-FED, 4-food elimination diet; qw, once a week; RCT, randomized controlled trial.
[a]Studies used different cut-off values ranging from 0 to < 15 eos/high-power field.
[b]Weight-tiered dosing based on body weight, ≥ 5 kg to < 15 kg, ≥ 15 kg to < 30 kg, or ≥ 30 kg to < 60 kg.[79]

maintained on a high dose. In addition, PPIs can disturb the microbiome in the gut,[80] which may increase the risk of allergies in young children (Table 1).

STCs

There is currently 1 approved STC BOS in the USA for a 12-week EoE treatment in patients aged ≥ 11 years, at a dose of 2 mg twice daily (BID), with histologic remission of 38.0%–53.1%,[24] and 1 approved STC (budesonide orodispersible tablet [BOT]) in Europe for patients aged ≥ 18 years.[106] Before the recent approval of the BOS in pediatric patients, off-label topical steroid formulations (swallowed budesonide or fluticasone propionate) have typically been used for EoE, which induce histologic response in 64%–87% of patients,[74–76] with reduction in esophageal mucosal inflammation and eosinophil counts, as well as reduction of fibrosis progression and tolerable safety profiles.[42,74,75] Despite their relatively successful treatment outcomes, STCs have been associated with side effects such as occasional oral and esophageal candidiasis in both adult and pediatric patients.[81–86,107]

Although some of the potential side effects of short-term STC use in EoE are considered incidental and negligible, the cumulative impact of long-term STC use in pediatric patients with EoE is unclear. In both pediatric and adult patients treated with STCs, the rate of adrenal suppression (AS) was found to be 15.8% (n = 94/596) based on a systematic review.[108] According to 2 prospective studies and 1 retrospective study in pediatric patients who received STCs for ≥ 1 month, AS, as measured by the low-dose adrenocorticotropic hormone stimulation test, was observed in some children without clinically significant symptoms of AS.[87–89] Thus, the risk of clinically significant AS in the pediatric population is likely to be low, and future prospective studies evaluating the clinical impact of AS secondary to STCs are warranted. Nevertheless, clinicians should be aware of the risk of AS when managing children during illness and before anesthesia.[89] Of note, the frequency of AS, in addition to being dose-dependent,[109] can also result from the cumulative effect of additional chronic topical steroids (ie, topical to the skin, nasal, and/or inhaled) being used for concurrent comorbid allergic diseases.[89]

Before the BOS US Food and Drug Administration (FDA) approval in 2024, patients have been using either off-label fluticasone via metered-dose inhaler to swallow, or manually preparing an oral viscous budesonide by mixing with a viscous solution/powder (eg, sucralose, syrup).[110] Limited data are available on the costs of heterogeneous off-label STC use in pediatric EoE; however, cost analysis studies of adult patients in the USA offer insights into the burden and costs of off-label STCs. A telephone survey of compounding pharmacies in Michigan reported that the formulations, dose, and instructions for use of compounded oral viscous budesonides varied across pharmacies, with a mean cost of $75.40/mo and fewer than half of the pharmacies reporting insurance coverage for the formulation.[90] Also, a cost-effectiveness modeling study of adults with EoE in the USA estimated the expense for fluticasone as $9262 and budesonide as $21,609 per person per 5-year horizon, discounted at 3% per year after the first year (vs 6-FED [$5720]) from the payer perspective.[91] Of note, initial treatment cost with fluticasone (an average of $1078 over a 1-year time horizon) was modestly less than EGD with dilation (an average of $1171) in another cost analysis model.[92] Although a prospective study demonstrated the safe and effective use of swallowed fluticasone, with a mean follow-up period of 20.4 months,[82] further studies are needed to better understand the risks of longer-term use of off-label STCs in children with EoE. The cost effectiveness of the approved BOS is currently unclear.

Overall, off-label use of STCs may increase the risk of oral or esophageal candidiasis, elevate the risk of AS particularly in children with EoE who are concomitantly using multiple forms of steroids (eg, patients with moderate-to-severe comorbid asthma, allergic rhinitis, or atopic dermatitis) for a long period, and accumulate treatment burden. Additionally, the potential side effects of the newly approved BOS include respiratory tract infection, gastrointestinal mucosal candidiasis, headache, gastroenteritis, throat irritation, AS, and erosive esophagitis (Table 1).[24,81–85,87–92]

Esophageal Dilation

Esophageal balloon dilation and Savary dilation are the options available as an adjunct treatment of severe dysphagia in children with fibrostenotic complications.[5,64,65] If needed, dilation is performed in conjunction with dietary elimination therapy or STCs.[64] A meta-analysis demonstrated that a median of 3 dilations led to symptom improvement in 95% of patients of all ages, with < 1% rates of perforation and hemorrhage.[77] However, 74% of patients reported chest pain following the procedure.[93] Although dilation is safe and effective, the need for multiple dilations, postprocedural pain, and lack of reduction of esophageal inflammation may contribute to long-term drawbacks (Table 1).[93,94] Additionally, the cost of endoscopy for dilation could be a treatment burden, with an estimated total cost of $9390.79 for 11 sedated EGDs in children.[94]

Dupilumab

Dupilumab is a fully human VelocImmune-derived[111,112] monoclonal antibody that blocks the shared interleukin (IL)-4 receptor α subunit for IL-4 and IL-13, inhibiting signaling of both IL-4 and IL-13, essential drivers of type 2 inflammation.[113,114] Blocking IL-4 receptor α inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and immunoglobulin E.[113–115] Dupilumab is approved for the treatment of multiple type 2 inflammatory diseases, including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, EoE, and prurigo nodularis.[26,27]

Dupilumab is the first and only biologic approved in the USA to treat EoE for adult and pediatric patients ≥ 1 year old, weighing ≥ 15 kg.[26] The initial US FDA approval in May 2022 for patients aged ≥ 12 years was based on the phase 3 LIBERTY EoE TREET study. At week 52, 85% of patients who received dupilumab at a weekly dose of 300 mg since baseline, and 68% of those who received placebo from baseline until week 24 and switched to a weekly dose of dupilumab, achieved histologic remission (≤6 eos/high-power field).[78] Dupilumab treatment also improved symptomatic, endoscopic, and molecular aspects after 24 weeks of treatment, which were sustained or continued to improve to week 52 in both adults and adolescents.[78] The most common adverse event was injection-site reaction; such reactions did not lead to discontinuation of dupilumab.[78,116]

The US FDA expanded the indication for younger children (1–11 years old) with EoE in January 2024 based on the ongoing phase 3 EoE KIDS study (Part A, 16-week double-blind treatment; Part B, 36-week extended active treatment; Part C, up to 108-week open-label extension period; NCT04394351). At week 16 in Part A, 68% of children on higher-dose dupilumab and 58% of children on lower-dose dupilumab at tiered dosing regimens based on weight achieved the primary endpoint of histologic remission vs 3% of children on placebo.[79] The higher-exposure dupilumab led to significant improvements in histologic, endoscopic, and transcriptomic measures.[79] The improvements in histologic, endoscopic, and transcriptomic measures between baseline and week 52 in all the patients were generally similar to the improvements between baseline and week 16 in the patients who received dupilumab in Part A.[79] Furthermore, higher-dose dupilumab numerically improved symptom burden, evaluated by caregivers using the Pediatric EoE Signs/Symptoms Questionnaire-Caregiver version at week 16, and continuous improvement was seen over 1 year of treatment with dupilumab.[79] The safety profile observed through 16 weeks in children aged 1–11 years was generally similar to the safety profile in adult and pediatric patients ≥ 12 years old observed through 24 weeks. The most common adverse events (≥2%) more frequently observed with dupilumab than placebo were injection-site reaction, upper respiratory tract infections, arthralgia, and herpes viral infections.[26] In EoE KIDS Part B, 1 case of helminth infection was reported in the dupilumab arm.[26]

Importantly, dupilumab use in EoE has been discussed by experts considering the current treatment algorithm for EoE.[23] Because the US FDA approved dupilumab in EoE without requiring failed response to other available treatments (PPIs, dietary therapies, STCs),[26] dupilumab may be considered as a first-line treatment in pediatric patients with EoE after taking into account the severity of their comorbid allergic diseases, if present, and their preferences.[23] However, in the LIBERTY EoE TREET and EoE KIDS studies, all patients had PPI-refractory disease and more than 30% had previously tried other available therapies including diets or steroids,[78,79] suggesting that dupilumab could also be used in patients refractory to other treatments.[23]

Although experts' clinical guidance has been provided on the use of dupilumab in patients ≥ 12 years old,[23] whether dupilumab is superior to other available therapies in EoE remains unknown. The availability of generic formulations of PPIs as tablets/capsules or suspensions[117] may mean they are perceived as a more convenient treatment option than dupilumab. The same may hold true for some STC formulations, although low adherence rates to STCs were observed in adolescents.[45] Furthermore, while data on the cost of dupilumab are not available, dupilumab is likely to be the most expensive EoE treatment compared with other therapies.[23] It is important to note that the long-term efficacy and safety profile of dupilumab in EoE has been demonstrated regardless of prior STC use or inadequate response, intolerance, and/or contraindication to STCs in adults and adolescents,[118] although the treatment impact and safety of dupilumab beyond a 1-year period in pediatric patients as young as 1 year old with EoE still need to be elucidated.

STCs and Biologics in Clinical Development for Pediatric EoE

A variety of novel STCs and biologics are undergoing clinical development for pediatric EoE (Table 2).

APT-1011 is an orally disintegrating tablet formulation of fluticasone. In the FLUTE phase 2b study (FLUTE-2), APT-1011 (4 regimens: 1.5 mg hora somni [at bedtime; HS], 1.5 mg BID, 3.0 mg HS, 3.0 mg BID) led to histologic, endoscopic, and symptomatic improvements at week 12 vs placebo that were sustained up to week 52 in adults with EoE.[107] A phase 3 study in adults with EoE, the FLUTE-3 study (NCT05634746) is ongoing to evaluate the efficacy and safety of APT-1011 3.0 mg HS for the induction of response to treatment over 24 weeks.[120] A substudy of FLUTE-2, the FLUTEEN study (3.0 mg HS) in pediatric patients aged ≥ 12 to < 18 years (NCT05083312) enrolled patients with histologically confirmed EoE (≥15 peak eos/high-power field) who had a history of ≥ 6 episodes of dysphagia in the 14 days before baseline. The primary endpoints are histologic responder rates (≤6 eos/high-power field) at week 12 and mean change from baseline to week 12 in number of dysphagia episodes. Secondary endpoints include mean change in Eosinophilic Esophagitis Endoscopic Reference Score (EREFS) from week 0 to week 12, percentage of patients with < 1 peak eos/high-power field at week 12, and mean change in Patient Reported Outcomes Symptoms score.[28]

BOS (2.0 mg/mL) is also undergoing clinical development. In a phase 3 induction study, 1.0 mg of BOT BID for 6 weeks led to clinical-histologic remission in adults with EoE[86]; maintenance of the clinical-histologic remission was demonstrated at 48 weeks following 1.0 mg or 0.5 mg of BOT in adults with EoE.[85] The phase 2/3 PEDEOS-1 study (EudraCT#2017-003737-29) is ongoing for children aged ≥ 2 to < 18 years with EoE. The study is enrolling pediatric

Table 2. STCs and Biologics in Clinical Development for Pediatric EoE

Drug[a]	Target/MOA	Summary of drug efficacy[a] reported in clinical trials of EoE	Summary of drug safety[a] reported in clinical trials of EoE	Ongoing clinical trial	Study population	
					Children	Adolescents and adults
Fluticasone propionate oral dispersible tablet formation (APT-1011)	Localized immune suppression (STCs)	• Phase 2b: Histologic response with APT-1011 (80.0% for 3.0 mg BID; 67.0% for 3.0 mg at bedtime [HS]; 86.0% for 1.5 mg BID; 48.0% for 1.5 mg HS) at wk 12, which was sustained through wk 52 in adults[107] • Endoscopic and symptomatic improvements at wk 12, which were sustained up to wk 52 in adults[107]	• Nasopharyngitis[107] • Oral and esophageal candidiasis[107]	Phase 3 FLUTEEN (a substudy of the FLUTE-2 trial, NCT05083312)[28]	—	Aged ≥ 12 to < 18 y
Budesonide oral suspension	Localized immune suppression (STCs)	• Phase 3: Induction of clinical and histologic remission with BOT 1.0 mg BID (58.0%) at wk 6 in adults[86] • Phase 3: Maintenance of clinical and histologic remission with BOT (73.5% for 0.5 mg BID; 75.0% for 1.0 mg BID) at wk 48 in adults[85]	• Oral and esophageal candidiasis[86]	Phase 2/3 study (EudraCT#:2017-003737-29)[29]	Aged ≥ 2 to < 18 y	—
Cendakimab	*IL-13* Binds to the IL-13 ligand, inhibits binding to IL-13Rα1 and IL-13Rα2 subunits	• Phase 2: Histologic response with cendakimab (94.8% for 180 mg qw; 99.9% for 360 mg qw) at wk 16 in adults[119] • Endoscopic improvement at wk 16 in adults[119]	• Headache[119] • Upper respiratory tract infection[119]	Phase 3 (NCT04753697)[30]	—	Aged ≥ 12 to ≤ 75 y
Tezepelumab	*Anti-TSLP* Binds to TSLP and blocks its interaction with the heterodimeric TSLP receptor	—	—	Phase 3 (NCT05583227)[31]	—	Aged ≥ 12 to ≤ 80 y

MOA, mechanism of action; qw, once a week; R, receptor; TSLP, thymic stromal lymphopoietin.
[a]Investigational agents.

patients with clinico-pathologic diagnosis of EoE who have clinically and histologically active EoE and an indication for treatment with a steroid. The primary endpoint is rate of patients with both pathologic remission and clinical response at week 12. Secondary endpoints include rate of patients with histologic remission at week 12 and rate of patients with clinical response at week 12.[29]

Cendakimab (RPC 4046/CC-93538) is a humanized monoclonal antibody that blocks IL-13 binding to the receptor subunits IL-13Rα1 and IL-13Rα2.[119] In a phase 2 study, cendakimab treatment at a dose of 180 mg or 360 mg subcutaneous once a week led to histologic and endoscopic improvements, but no statistically significant reduction of dysphagia clinical score at week 16 in adults with EoE.[119] At a 360 mg dose of cendakimab, significant reductions in endoscopic severity score, histologic grade and stage scores, and clinician's global assessment of disease severity were observed at week 16.[119] A phase 3 study of cendakimab at a dose of 360 mg subcutaneous (NCT04753697) is ongoing for patients aged $\geq$ 12 and $\leq$ 75 years. The study is enrolling patients with histologic evidence of EoE ($\geq$15 peak eos/high-power field) who reported history of $\geq$ 4 dysphagia days within 2 consecutive weeks before end of screening. The primary endpoints are clinical response (mean change in dysphagia days) and histologic response ($\leq$6 eos/high-power field) at week 24. Secondary endpoints include histologic response ($<$15 eos/high-power field), change from baseline in EREFS, and change from baseline in Eosinophilic Esophagitis Histology Scoring System grade and stage scores at week 24.[30]

Tezepelumab is a human monoclonal antibody that binds to thymic stromal lymphopoietin and blocks its interaction with the heterodimeric thymic stromal lymphopoietin receptor. While clinical data in EoE are lacking, tezepelumab is approved for add-on maintenance treatment of adult and pediatric patients aged $\geq$ 12 years with severe asthma.[121] The phase 3 CROSSING study of tezepelumab at a high or low subcutaneous dose (NCT05583227) is ongoing for patients aged $\geq$ 12 and $\leq$ 80 years. The study is enrolling patients with a previous EGD and an esophageal biopsy confirming a diagnosis of EoE. Patients who have symptomatic EoE (as defined by a history of on average of $\geq$ 2 episodes of dysphagia per week within the 4 weeks before the first visit of the study) are being included. The primary endpoints are histologic response ($\leq$6 eos/high-power field) and change from baseline in Dysphagia Symptom Questionnaire score at week 24. Secondary endpoints include change from baseline in EoE EREFS and Eosinophilic Esophagitis Histology Scoring System grade and stage scores at week 24.[31]

Conclusion

EoE is a chronic, progressive, type 2 inflammatory condition that can present at any age during one's life, bringing a significant burden to pediatric patients. In young children, nonspecific symptoms and feeding difficulties substantially affect children's eating skills and growth, as well as the psychosocial and financial domains of QOL in both patients and their caregivers. In adolescents, chronic symptoms of dysphagia and food impaction are associated with anxiety and negative impacts on their daily feeding and social life. In pediatric EoE, diagnostic delay ranges from 1 to 4 years and may lead to persistent esophageal inflammation and increased risk of esophageal fibrostenosis, further adding to the symptom burden. Current treatment options can be effective but may not provide long-term comprehensive disease control or may have uncertain long-term side effects. Overall, the burden of pediatric EoE is carried by both patients and caregivers, impacting the psychosocial, emotional, and financial aspects of their lives. Thus, comprehensive evaluation of nonspecific symptoms of EoE in clinical practice, timely referral to specialists familiar with managing EoE, and development of novel targeted therapies that can modify the disease are needed. With newly approved therapies and products in the pipeline, greater understanding of the pathophysiology and the various phenotypes of EoE is warranted, so that tailored therapies can be used to reduce the disease burden for patients and their caregivers.

References

1. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018; 154:319–332.e3.
2. Bredenoord AJ, Patel K, Schoepfer AM, et al. Disease burden and unmet need in eosinophilic esophagitis. Am J Gastroenterol 2022;117:1231–1241.
3. Chehade M, Jones SM, Pesek RD, et al. Phenotypic characterization of eosinophilic esophagitis in a large multicenter patient population from the consortium for food allergy research. J Allergy Clin Immunol Pract 2018; 6:1534–1544.e5.
4. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr 2009;48:30–36.
5. Visaggi P, Savarino E, Sciume G, et al. Eosinophilic esophagitis: clinical, endoscopic, histologic and therapeutic differences and similarities between children and adults. Therap Adv Gastroenterol 2021;14: 1756284820980860.
6. Navarro P, Arias A, Arias-Gonzalez L, et al. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther 2019;49:1116–1125.
7. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230–1236.e1-2.
8. Chang NC, Thakkar KP, Ketchem CJ, et al. A gap in care leads to progression of fibrosis in eosinophilic esophagitis patients. Clin Gastroenterol Hepatol 2022; 20:1701–1708.e2.
9. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, et al. The natural course of eosinophilic esophagitis and

long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol 2018;113:836–844.
10. Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. J Clin Gastroenterol 2016;50:134–140.
11. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–585.e4.
12. Koutlas NT, Dellon ES. Progression from an inflammatory to a fibrostenotic phenotype in eosinophilic esophagitis. Case Rep Gastroenterol 2017;11:382–388.
13. Mehta P, Furuta GT, Brennan T, et al. Nutritional state and feeding behaviors of children with eosinophilic esophagitis and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2018;66:603–608.
14. Wu YP, Franciosi JP, Rothenberg ME, et al. Behavioral feeding problems and parenting stress in eosinophilic gastrointestinal disorders in children. Pediatr Allergy Immunol 2012;23:730–735.
15. Haas AM, Maune NC. Clinical presentation of feeding dysfunction in children with eosinophilic gastrointestinal disease. Immunol Allergy Clin North Am 2009;29:65–75, ix.
16. Chehade M, Meyer R, Beauregard A. Feeding difficulties in children with non-IgE-mediated food allergic gastrointestinal disorders. Ann Allergy Asthma Immunol 2019;122:603–609.
17. Harris RF, Menard-Katcher C, Atkins D, et al. Psychosocial dysfunction in children and adolescents with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2013;57:500–505.
18. Hannan N, McMillan SS, Tiralongo E, et al. Treatment burden for pediatric eosinophilic esophagitis: a cross-sectional survey of carers. J Pediatr Psychol 2021;46:100–111.
19. Klinnert MD, Silveira L, Harris R, et al. Health-related quality of life over time in children with eosinophilic esophagitis and their families. J Pediatr Gastroenterol Nutr 2014;59:308–316.
20. Wechsler JB, Schwartz S, Amsden K, et al. Elimination diets in the management of eosinophilic esophagitis. J Asthma Allergy 2014;7:85–94.
21. Greuter T, Bussmann C, Safroneeva E, et al. Long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concept. Am J Gastroenterol 2017;112:1527–1535.
22. Steinbach EC, Hernandez M, Dellon ES. Eosinophilic esophagitis and the eosinophilic gastrointestinal diseases: approach to diagnosis and management. J Allergy Clin Immunol Pract 2018;6:1483–1495.
23. Aceves SS, Dellon ES, Greenhawt M, et al. Clinical guidance for the use of dupilumab in eosinophilic esophagitis: a yardstick. Ann Allergy Asthma Immunol 2023;130:371–378.
24. US Food and Drug Administration. EOHILIA™ (budesonide oral suspension). Highlights of prescribing information. https://content.takeda.com/?contenttype=PI&product=EOH&language=ENG&country=USA&documentnumber=1. Accessed July 16, 2024.
25. Leung J, Mehrzad R, Hundal NV, et al. Longitudinal perspective on managing refractory eosinophilic esophagitis. J Allergy Clin Immunol Pract 2015;3:951–956.
26. US Food and Drug Administration. DUPIXENT® (dupilumab). Highlights of prescribing information. https://www.regeneron.com/downloads/dupixent_fpi.pdf. Accessed July 16, 2024.
27. European Medicines Agency. DUPIXENT® (dupilumab). Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. Accessed July 16, 2024.
28. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05083312?term=NCT05083312&rank=1&limit=10. Accessed July 16, 2024.
29. Clinicaltrialsregister.eu. https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003737-29/DE. Accessed July 16, 2024.
30. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT04753697?term=NCT04753697&rank=1&limit=10. Accessed July 16, 2024.
31. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05583227?term=NCT05583227&rank=1&limit=10. Accessed July 16, 2024.
32. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5:335–358.
33. Gomez Torrijos E, Gonzalez-Mendiola R, Alvarado M, et al. Eosinophilic esophagitis: review and update. Front Med (Lausanne) 2018;5:247.
34. Liacouras CA, Spergel J, Gober LM. Eosinophilic esophagitis: clinical presentation in children. Gastroenterol Clin North Am 2014;43:219–229.
35. Barni S, Arasi S, Mastrorilli C, et al. Pediatric eosinophilic esophagitis: a review for the clinician. Ital J Pediatr 2021;47:230.
36. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology 2018;155:1022–1033.e10.
37. Oliva S, Dias JA, Rea F, et al. Characterization of eosinophilic esophagitis from the European Pediatric Eosinophilic Esophagitis Registry (pEEr) of ESPGHAN. J Pediatr Gastroenterol Nutr 2022;75:325–333.
38. Shaheen NJ, Mukkada V, Eichinger CS, et al. Natural history of eosinophilic esophagitis: a systematic review of epidemiology and disease course. Dis Esophagus 2018;31:doy01.
39. Muir AB, Brown-Whitehorn T, Godwin B, et al. Eosinophilic esophagitis: early diagnosis is the key. Clin Exp Gastroenterol 2019;12:391–399.
40. Votto M, Lenti MV, De Silvestri A, et al. Evaluation of diagnostic time in pediatric patients with eosinophilic gastrointestinal disorders according to their clinical features. Ital J Pediatr 2023;49:9.
41. Hoofien A, Rea F, Espinheira MDC, et al. Systemic steroids have a role in treating esophageal strictures in pediatric eosinophilic esophagitis. Dig Liver Dis 2021;53:324–328.

42. Ruffner MA, Spergel JM. Pediatric eosinophilic esophagitis: updates for the primary care setting. Curr Opin Pediatr 2018;30:829–836.
43. Menard-Katcher C, Benitez AJ, Pan Z, et al. Influence of age and eosinophilic esophagitis on esophageal distensibility in a pediatric cohort. Am J Gastroenterol 2017; 112:1466–1473.
44. Lieberman JA, Morotti RA, Konstantinou GN, et al. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. Allergy 2012;67:1299–1307.
45. Mehta P, Pan Z, Skirka S, et al. Medication adherence aligns with age and a behavioral checklist but not symptoms or quality of life for patients with eosinophilic esophagitis. J Pediatr 2021;235:246–252.e1.
46. Votto M, Castagnoli R, De Filippo M, et al. Behavioral issues and quality of life in children with eosinophilic esophagitis. Minerva Pediatr 2020;72:424–432.
47. Lynch MK, Dimmitt RA, Goodin BR. Evidence of disturbed sleep in children with eosinophilic esophagitis and persistent epigastric pain. J Pediatr Psychol 2018; 43:331–341.
48. Paquet B, Begin P, Paradis L, et al. High rate of failure to thrive in a pediatric cohort with eosinophilic esophagitis. Ann Allergy Asthma Immunol 2016;116:73–74.e1.
49. Azzano P, Villard Truc F, Collardeau-Frachon S, et al. Children with eosinophilic esophagitis in real life: 10 years' experience with a focus on allergic management. Allergol Immunopathol 2020;48:244–250.
50. Hoofien A, Dias JA, Malamisura M, et al. Pediatric eosinophilic esophagitis: results of the European Retrospective Pediatric Eosinophilic Esophagitis Registry (RetroPEER). J Pediatr Gastroenterol Nutr 2019; 68:552–558.
51. Klinnert MD. Psychological impact of eosinophilic esophagitis on children and families. Immunol Allergy Clin North Am 2009;29:99–107, x.
52. Jensen ET, Kappelman MD, Martin CF, et al. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. Am J Gastroenterol 2015;110:626–632.
53. Schwartz S, Manuel-Rubio M, Shaykin R, et al. Cost comparison of steroids vs different elimination diet for the treatment of eosinophilic esophagitis in children. JPGN 2016;63:S1–S415.
54. Eke R, Dellon ES. Hospitalization trends and determinants of inpatient costs for eosinophilic esophagitis patients in the United States: results from the Nationwide Inpatient Sample analysis. Ann Gastroenterol 2021; 34:643–650.
55. Dellon ES. Cost-effective care in eosinophilic esophagitis. Ann Allergy Asthma Immunol 2019;123:166–172.
56. Anderson J, Moonie S, Hogan MB, et al. Cost of chronic inflammatory disease: the impact of eosinophilic esophagitis in Nevada. J Dig Dis 2020;21:12–19.
57. Fan T, Aggarwal J, Jiang J, et al. S390. Estimating the indirect and intangible costs associated with eosinophilic esophagitis. Am J Gastroenterol 2021;116: S171–S172.
58. Anderson GF, Hussey P, Petrosyan V. It's still the prices, stupid: why the US spends so much on health care, and a tribute to Uwe Reinhardt. Health Aff 2019;38:87–95.
59. Gunja MZ, Gumas ED, Williams II RD. U.S. health care from a global perspective, 2022: accelerating spending, worsening outcomes. The Commonwealth Fund. 2023. https://www.commonwealthfund.org/publications/issue-briefs/2023/jan/us-health-care-global-perspective-2022. Accessed July 16, 2024.
60. Robinson J, Furuta GT, Hadker N, et al. Transition of care from pediatric to adult care in eosinophilic esophagitis: insights from a patient perspective survey. J Pediatr Gastroenterol Nutr 2021;73:722–726.
61. Dellon ES, Jones PD, Martin NB, et al. Health-care transition from pediatric to adult-focused gastroenterology in patients with eosinophilic esophagitis. Dis Esophagus 2013;26:7–13.
62. Eluri S, Book WM, Kodroff E, et al. Lack of knowledge and low readiness for health care transition in eosinophilic esophagitis and eosinophilic gastroenteritis. J Pediatr Gastroenterol Nutr 2017;65:53–57.
63. Hiremath G, Chapa-Rodriguez A, Katzka DA, et al. Transition of care of patients with eosinophilic gastrointestinal diseases: challenges and opportunities. Transl Sci Rare Dis 2022;6:13–23.
64. Robles-Medranda C, Villard F, le Gall C, et al. Severe dysphagia in children with eosinophilic esophagitis and esophageal stricture: an indication for balloon dilation? J Pediatr Gastroenterol Nutr 2010;50:516–520.
65. Al-Hussaini A. Savary dilation is safe and effective treatment for esophageal narrowing related to pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2016;63:474–480.
66. Chehade M, Brown S. Elimination diets for eosinophilic esophagitis: making the best choice. Expert Rev Clin Immunol 2020;16:679–687.
67. Arias A, Gonzalez-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014; 146:1639–1648.
68. Markowitz J. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003;98:777–782.
69. Groetch M, Venter C, Skypala I, et al. Dietary therapy and nutrition management of eosinophilic esophagitis: a work group report of the American Academy of Allergy, Asthma, and Immunology. J Allergy Clin Immunol Pract 2017;5:312–324.e29.
70. Nguyen N, Kramer RE, Menard-Katcher C. Endoscopy in pediatric eosinophilic esophagitis. Front Pediatr 2021;9: 713027.
71. Schultz F, Warren CM, Chehade M, et al. When supplemental formula is essential: overcoming barriers to hypoallergenic formula access for patients with food allergies. J Allergy Clin Immunol Pract 2023;11:2686–2692.
72. Asher Wolf W, Huang KZ, Durban R, et al. The six-food elimination diet for eosinophilic esophagitis increases grocery shopping cost and complexity. Dysphagia 2016; 31:765–770.
73. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:13–22.e1.

74. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of budesonide vs fluticasone for initial treatment of eosinophilic esophagitis in a randomized controlled trial. Gastroenterology 2019;157:65–73.e5.
75. Aceves SS, Bastian JF, Newbury RO, et al. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol 2007; 102:2271–2279; quiz 2280.
76. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010;139:418–429.
77. Moawad FJ, Molina-Infante J, Lucendo AJ, et al. Systematic review with meta-analysis: endoscopic dilation is highly effective and safe in children and adults with eosinophilic oesophagitis. Aliment Pharmacol Ther 2017; 46:96–105.
78. Rothenberg ME, Dellon ES, Collins MH, et al. Efficacy and safety of dupilumab up to 52 weeks in adults and adolescents with eosinophilic oesophagitis (LIBERTY EoE TREET study): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2023;8:990–1004.
79. Chehade M, Dellon ES, Spergel JM, et al. Dupilumab for eosinophilic esophagitis in patients 1 to 11 years of age. N Engl J Med 2024;390:2239–2251.
80. Castellani C, Singer G, Kashofer K, et al. The influence of proton pump inhibitors on the fecal microbiome of infants with gastroesophageal reflux-a prospective longitudinal interventional study. Front Cell Infect Microbiol 2017;7:444.
81. Nennstiel S, Schlag C. Treatment of eosinophilic esophagitis with swallowed topical corticosteroids. World J Gastroenterol 2020;26:5395–5407.
82. Andreae DA, Hanna MG, Magid MS, et al. Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. Am J Gastroenterol 2016;111:1187–1197.
83. Chuang MY, Chinnaratha MA, Hancock DG, et al. Topical steroid therapy for the treatment of eosinophilic esophagitis (EoE): a systematic review and meta-analysis. Clin Transl Gastroenterol 2015;6:e82.
84. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol 2008; 6:165–173.
85. Straumann A, Lucendo AJ, Miehlke S, et al. Budesonide orodispersible tablets maintain remission in a randomized, placebo-controlled trial of patients with eosinophilic esophagitis. Gastroenterology 2020;159:1672–1685.e5.
86. Lucendo AJ, Miehlke S, Schlag C, et al. Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic esophagitis in a randomized placebo-controlled trial. Gastroenterology 2019;157:74–86.e15.
87. Ahmet A, Benchimol EI, Goldbloom EB, et al. Adrenal suppression in children treated with swallowed fluticasone and oral viscous budesonide for eosinophilic esophagitis. Allergy Asthma Clin Immunol 2016;12:49.
88. Golekoh MC, Hornung LN, Mukkada VA, et al. Adrenal insufficiency after chronic swallowed glucocorticoid therapy for eosinophilic esophagitis. J Pediatr 2016; 170:240–245.
89. Harel S, Hursh BE, Chan ES, et al. Adrenal suppression in children treated with oral viscous budesonide for eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2015;61:190–193.
90. Joshi S, Rubenstein JH, Dellon ES, et al. Variability in practices of compounding budesonide for eosinophilic esophagitis. Am J Gastroenterol 2021;116:1336–1338.
91. Cotton CC, Erim D, Eluri S, et al. Cost utility analysis of topical steroids compared with dietary elimination for treatment of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2017;15:841–849.e1.
92. Kavitt RT, Penson DF, Vaezi MF. Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy. Dis Esophagus 2014; 27:418–423.
93. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. Am J Gastroenterol 2010;105:1062–1070.
94. Friedlander JA, DeBoer EM, Soden JS, et al. Unsedated transnasal esophagoscopy for monitoring therapy in pediatric eosinophilic esophagitis. Gastrointest Endosc 2016;83:299–306.e1.
95. Gutierrez-Junquera C, Fernandez-Fernandez S, Cilleruelo ML, et al. High prevalence of response to proton-pump inhibitor treatment in children with esophageal eosinophilia. J Pediatr Gastroenterol Nutr 2016; 62:704–710.
96. Dohil R, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical subphenotype of pediatric eosinophilic esophagitis. Dig Dis Sci 2012;57:1413–1419.
97. Schroeder S, Capocelli KE, Masterson JC, et al. Effect of proton pump inhibitor on esophageal eosinophilia. J Pediatr Gastroenterol Nutr 2013;56:166–172.
98. Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, et al. Long-term treatment with proton pump inhibitors is effective in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2018; 67:210–216.
99. Wang YH, Wintzell V, Ludvigsson JF, et al. Association between proton pump inhibitor use and risk of asthma in children. JAMA Pediatr 2021;175:394–403.
100. Mitre E, Susi A, Kropp LE, et al. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. JAMA Pediatr 2018;172:e180315.
101. Levy EI, Hoang DM, Vandenplas Y. The effects of proton pump inhibitors on the microbiome in young children. Acta Paediatr 2020;109:1531–1538.
102. Barron JJ, Tan H, Spalding J, et al. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr 2007;45:421–427.
103. Chen IL, Gao WY, Johnson AP, et al. Proton pump inhibitor use in infants: FDA reviewer experience. J Pediatr Gastroenterol Nutr 2012;54:8–14.
104. Hufnagl K, Pali-Scholl I, Roth-Walter F, et al. Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol 2020;42:75–93.

105. Untersmayr E, Bakos N, Scholl I, et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J 2005;19:656–658.
106. European Medicines Agency. Jorveza (budesonide orodispersible tablet). Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/jorveza-epar-product-information_en.pdf. Accessed July 16, 2024.
107. Dellon ES, Lucendo AJ, Schlag C, et al. Fluticasone propionate orally disintegrating tablet (APT-1011) for eosinophilic esophagitis: randomized controlled trial. Clin Gastroenterol Hepatol 2022;20:2485–2494.e15.
108. Philpott H, Dougherty MK, Reed CC, et al. Systematic review: adrenal insufficiency secondary to swallowed topical corticosteroids in eosinophilic oesophagitis. Aliment Pharmacol Ther 2018;47:1071–1078.
109. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999;159:941–955.
110. Alexander JA. Topical steroid therapy for eosinophilic esophagitis. Gastroenterol Hepatol 2014;10:327–329.
111. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A 2014;111:5147–5152.
112. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A 2014;111:5153–5158.
113. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol 2017;13:425–437.
114. Gandhi NA, Bennett BL, Graham NM, et al. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov 2016;15:35–50.
115. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Ralpha antibody, is required to broadly inhibit type 2 inflammation. Allergy 2020;75:1188–1204.
116. Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. N Engl J Med 2022;387:2317–2330.
117. Wensel TM. Administration of proton pump inhibitors in patients requiring enteral nutrition. P T 2009;34:143–160.
118. Bredenoord AJ, Dellon E, Hirano I, et al. Dupilumab demonstrated efficacy and was well tolerated regardless of prior use of swallowed topical corticosteroids in adolescent and adult patients with eosinophilic oesophagitis: a subgroup analysis of the phase 3 LIBERTY EoE TREET study. Gut 2023;73:398–406.
119. Hirano I, Collins MH, Assouline-Dayan Y, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients with eosinophilic esophagitis. Gastroenterology 2019;156:592–603.e10.
120. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05634746?cond=eosinophilic%20esophagitis&intr=APT-1011&rank=3. Accessed July 16, 2024.
121. US Food and Drug Administration. TEZSPIRE® (tezepelumab-ekko). Highlights of prescribing information. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/e306dc06-d580-4457-b15f-9f28545ad63a/e306dc06-d580-4457-b15f-9f28545ad63a_viewable_rendition__v.pdf. Accessed July 16, 2024.

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Conflicts of Interest:
The authors disclose the following: Mirna Chehade has served as a consultant for Adare Pharma Solutions/Ellodi Pharmaceuticals, Allakos, AstraZeneca, Bristol Myers Squibb, Nexstone Immunology, Phathom, Recludix Pharma, Regeneron Pharmaceuticals Inc, Sanofi, and Shire/Takeda, and has received research funding from Adare Pharma Solutions/Ellodi Pharmaceuticals, Allakos, AstraZeneca, Celgene/Bristol Myers Squibb, Danone, Regeneron Pharmaceuticals Inc, and Shire/Takeda. Girish S. Hiremath is a consultant for Bristol Myers Squibb, Regeneron Pharmaceuticals Inc, and Sanofi. Noam Zevit is a consultant for Adare Pharmaceuticals, AstraZeneca, Dr Falk Pharma, Rafa Inc, Regeneron Pharmaceuticals Inc, and Sanofi, and has received speaker fees from Dr Falk Pharma, Rafa Inc, Regeneron Pharmaceuticals Inc, and Sanofi. Salvatore Oliva is a consultant for Celgene/Receptos/Bristol Myers Squibb, Medtronic, Ocean Pharma, and Sanofi/Regeneron Pharmaceuticals Inc, and has received speaker fees from Medtronic and Sanofi. Tiffany Pela and Juby Jacob-Nara are employees of Sanofi and may hold stock and/or stock options in the company. Angela Khodzhayev and Amr Radwan are employees and shareholders of Regeneron Pharmaceuticals Inc.

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