



Improving Care in Eosinophil-Associated Diseases: A Charter

David J. Jackson · Praveen Akuthota · Rebeca Andradas ·
Albert J. Bredenoord · Amanda Cordell · Sarah Gray · Joyce Kullman ·
Sameer K. Mathur · Ian Pavord · Florence Roufosse · Christian Rubio ·
Irena Clisson Rusek · Dagmar Simon · Mary Jo Strobel ·
Tonya Winders

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ABSTRACT

Eosinophil-associated diseases (EADs) are a range of heterogeneous conditions in which eosinophils are believed to play a critical pathological role. EADs include common illnesses such as eosinophilic asthma and chronic rhinosinusitis and rare conditions such as hypereosinophilic syndromes (HES) and eosinophilic gastrointestinal disorders (EGIDs). EADs are associated with substantial burdens for the patient, including chronic, debilitating

symptoms, increased financial burden, decreased health-related quality of life, and the need for repeated visits to multiple different healthcare professionals (HCPs), emergency departments, and/or hospitals. Poor EAD recognition by HCPs often contributes to delayed diagnoses, which further delays patient access to appropriate care and effective treatments, contributing to poor health outcomes. The objective of this charter is to outline key patient rights and expectations with respect to the management of their condition(s) and to set

D. J. Jackson (✉)
Guy's Severe Asthma Centre, Guy's Hospital, Guy's
and St Thomas' NHS Trust, School of Immunology
and Microbial Sciences, King's College London,
London SE1 9RT, UK
e-mail: David.Jackson@gstt.nhs.uk

D. J. Jackson
School of Immunology and Microbial Sciences,
King's College, London, UK

P. Akuthota
Division of Pulmonary, Critical Care, and Sleep
Medicine, Department of Medicine, University of
California San Diego, La Jolla, CA, USA

R. Andradas
Spanish Association of Eosinophilic Esophagitis-
AEDESEO, Madrid, Spain

A. J. Bredenoord
Department of Gastroenterology and Hepatology,
Amsterdam UMC, University of Amsterdam,
Amsterdam, The Netherlands

A. Cordell
EOS Network Eosinophilic Diseases Charity,
Colchester, England, UK

S. Gray
AusEE Inc., Queensland, Australia

J. Kullman
Vasculitis Foundation, Kansas City, MO, USA

S. K. Mathur
Division of Allergy, Pulmonary and Critical Care
Medicine, Department of Medicine, School of
Medicine and Public Health, University of
Wisconsin, Madison, WI, USA

I. Pavord
Oxford Respiratory NIHR BRC, Nuffield Department
of Medicine, University of Oxford, Oxford, UK

F. Roufosse
Department of Internal Medicine, Hôpital Erasme,
Université Libre de Bruxelles, Brussels, Belgium

forth an ambitious action plan to improve health outcomes for patients with EADs: (1) people with EADs, their caretakers, HCPs, and the public must have greater awareness and education about EADs; (2) people with EADs must receive a timely, accurate diagnosis; (3) all people with EADs must have access to an appropriate multidisciplinary team, when necessary; and (4) people with EADs must have access to safe and effective treatment options without unnecessary regulatory delays. The principles described in this charter demonstrate the core elements of quality care that people with EADs must receive, and they represent clear steps by which to reduce patient and caregiver burden and improve patient outcomes. We urge HCPs, healthcare systems, and policymakers worldwide to swiftly adopt these principles to ensure patients with EADs have an accurate diagnosis in a timely manner and access to high-level care and treatment in an appropriate setting.

Keywords: Eosinophil-associated diseases; Eosinophilic immune dysfunction (EID); Healthcare professional (HCP) education; Multidisciplinary teams (MDTs); Patient education; Patient rights; Timely diagnosis

C. Rubio
Global Genes, Boston, MA, USA

I. C. Rusek
Association Pour l'Information sur les Maladies à Eosinophiles-APIMEO, Bourg-la-Reine, France

D. Simon
Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

M. J. Strobel
American Partnership for Eosinophilic Disorders, Atlanta, GA, USA

T. Winders
Allergy and Asthma Network, Vienna, VA, USA

T. Winders
Global Allergy and Airways Patient Platform, Vienna, Austria

Key Summary Points

Eosinophil-associated diseases (EADs) represent a range of heterogeneous conditions in which eosinophils are believed to play a critical pathological role

Patients with EADs face substantial disease burdens, including debilitating symptoms and associated disease flares, and an arduous path to diagnosis and treatment, often involving repeated visits to multiple clinical subspecialties

This charter outlines key rights that patients should expect from the management of their condition(s) and describes an ambitious action plan to improve health outcomes for patients with EADs

Patients and their caretakers, multiple healthcare professionals, and the broader public need greater awareness and education about EADs

All patients with EADs deserve a timely and accurate diagnosis, access to an appropriate multidisciplinary team, and access to appropriate treatments

INTRODUCTION

The eosinophil is one of a number of white blood cells that make up the immune system [1]. In recent years, a range of inflammatory diseases have been identified across several organ systems and tissues that appear to be driven primarily by abnormal regulation of the number and/or activation state of eosinophils [2–6]. The term *eosinophilic immune dysfunction* (EID) has recently been used to describe the underlying roles of eosinophils in these respiratory, dermatological, gastrointestinal, and systemic conditions (Table 1) [6, 7]. The range of heterogeneous diseases in which eosinophils are believed to play a critical pathological role

Table 1 Information about various EADs (presented alphabetically)^a

Disease information	Estimated prevalence	Guidelines
<p>Atopic dermatitis (AD)</p> <p>Also known as eczema, AD is a common, heterogeneous, and recurrent chronic inflammatory skin disease, which is associated with other known allergic disorders, including asthma. Eosinophils play an active role in AD pathology, with the presence of eosinophil granule proteins in skin lesions. AD is characterised by acute flare-ups of pruritic lesions over dry skin and causes discomfort, which includes intense itching, sleep impairment, and impact on health-related quality of life (including concerns about aesthetics/physical appearance)</p>	<p>Prevalence estimates vary between 3.2–10.2% in the US [50]</p>	<p>American Academy of Dermatology Association Atopic Dermatitis Clinical Guideline</p> <p>European Academy of Dermatology and Venereology Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children: Part I</p> <p>European Academy of Dermatology and Venereology Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children: Part 2</p>
<p>Bullous pemphigoid (BP)</p> <p>BP is a rare autoimmune, chronic skin disorder characterised by blistering and/or urticarial lesions (hives) and itching, where patients often show high levels of eosinophils in peripheral blood and/or tissue lesions. It is associated with high morbidity and mortality. It typically affects elderly patients with an average patient age of 80 years old</p>	<p>7.63 per 100,000 patient-years in England [51]</p>	<p>British Association of Dermatologists' Guidelines on the Management of Bullous Pemphigoid (2012)</p>
<p>Chronic obstructive pulmonary disease (COPD)</p> <p>COPD is a progressive disease that can cause obstruction of airflow in the lungs, resulting in debilitating bouts of breathlessness. The COPD subset with eosinophil-driven inflammation phenotypes is characterised by elevated eosinophil counts in the blood or airways and accounts for 20% to 40% of patients with stable COPD. Improving lung function, reducing exacerbations, and managing daily symptoms, such as breathlessness, are important treatment goals in the management of COPD</p>	<p>384 million people worldwide (20%–40%) [52]</p>	<p>ATS Pharmacologic Management of COPD: An Official ATS Clinical Practice Guideline (2020)</p> <p>Global Initiative for Chronic Obstructive Lung Disease Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2021 Report (2020)</p>
<p>Chronic spontaneous urticaria (CSU)</p>		

Table 1 continued

Disease information	Estimated prevalence	Guidelines
<p>CSU is a dermatological condition in which hives, welts, or subcutaneous swellings occur lasting for > 6 weeks. Eosinophilic infiltration is common in patients with CSU, where signalling between activated eosinophils and mast cells in the skin leads to chronic inflammation. These hives—which range in size from just a few millimetres to several centimetres—are itchy and can occur anywhere on the body, including the face, extremities, chest, or back. CSU has a significant burden on a patient’s health-related quality of life, including sleep impairment and overall functioning</p>	<p>Global prevalence of 0.1–1.4% [53]</p>	<p>EAACI/GALEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria</p>
Eosinophilic asthma (EA)		
<p>EA is the most common type of asthma and is associated with high levels of eosinophils in the blood and airways, leading to daily asthma symptoms and the risk of life-threatening asthma attacks</p>	<p>Approximately 34 million worldwide have severe asthma, and estimates suggest ~ 50% of them have an eosinophilic phenotype [9, 29]</p>	<p>Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (2020) ERS/ATS Clinical Practice Guidelines on the Definition, Evaluation, and Treatment of Severe Asthma (2020)</p>
Eosinophilic bronchitis (EB)		
<p>Eosinophilic bronchitis (EB) is characterised by eosinophilic airway inflammation (similar to the airway inflammation in asthma) without associated airway hyperresponsiveness or variable airflow obstruction</p>		
Eosinophilic colitis		
<p>Eosinophilic colitis is a rare disease in the group of EGIDs. It is characterised by the presence of a dense eosinophilic infiltrate into the colonic wall; more often, patients present with abdominal pain or diarrhoea. Diagnosing the condition is challenging due to the lack of diagnostic guidelines and the use of a diagnostic process of exclusion where other causes of colonic eosinophilia are excluded first</p>	<p>Estimated prevalence of 3.3 per 100,000 in the US [36]</p>	
Eosinophilic cystitis (EC)		

Table 1 continued

Disease information	Estimated prevalence	Guidelines
<p>EC is a rare inflammatory bladder condition caused by the accumulation of eosinophils in the bladder. In patients with EC, eosinophilic inflammation of the bladder results in urinary frequency, painful urination, blood in the urine, and abdominal or pelvic pain</p>		
Eosinophilic duodenitis (EoD)	<p>Eosinophilic duodenitis is a chronic, inflammatory disease characterised by high levels of mast cells and eosinophils in the stomach and/or the duodenum, leading to symptoms that include chronic abdominal pain, nausea, bloating, loss of appetite, early satiety, abdominal cramping, vomiting, and diarrhoea</p>	<p>The estimated prevalence of EG/EoD is approximately 15 per 100,000 people, although this is likely an underestimate as misdiagnosis is common for these conditions [19]</p>
Eosinophilic esophagitis (EoE)	<p>A rare chronic, local, immune-mediated oesophageal disease, characterised clinically by symptoms related to oesophageal dysfunction associated with marked inflammation, including eosinophils. Dysregulated immune responses lead to recruitment and activation of eosinophils in the oesophagus, which results in injury, fibrosis, and dysfunction that can potentially lead to dysphagia and food impaction, chronic pain, difficulty swallowing, poor growth in children, malnutrition, and weight loss. The EoE diagnosis can be challenging to make in children, given that it requires invasive endoscopic assessment and biopsy with high-powered imaging</p>	<p>The estimated prevalence of EoE varies across sources: 23.1 per 100,000 patient-years [54] and 56.7 per 100,000 in the US [55]</p> <p>United European Gastroenterology Diagnosis and Management Guidelines for Eosinophilic Esophagitis</p> <p>AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis (2020)</p>
Eosinophilic fasciitis		

Table 1 continued

Disease information	Estimated prevalence	Guidelines
<p>Eosinophilic fasciitis is a rare condition characterised by inflammation of the band of fibrous tissue beneath the skin and surrounding the muscles (fascia), usually affecting the arms and legs. The inflammation is caused by the abnormal accumulation of certain white blood cells, including eosinophils, in the fascia. The accumulation of eosinophils eventually causes skin swelling and progressive thickening and hardening</p>		
<p>Eosinophilic dermatitis</p> <p>A broad, heterogeneous group of dermatological diseases that are characterised by eosinophil infiltration and/or degranulation in skin lesions with or without associated blood eosinophilia. Conditions classically described as eosinophilic dermatitis include eosinophilic cellulitis, eosinophilic fasciitis, eosinophilic folliculitis, cutaneous eosinophilic vasculitis, and granuloma faciale</p>		
<p>Eosinophilic gastritis (EG)</p> <p>Eosinophilic gastritis is a rare digestive condition characterised by eosinophilic infiltration of the stomach, which may lead to epigastric pain, nausea, and vomiting or, less frequently, signs of upper gastrointestinal bleeding. It can be an isolated condition or, more commonly, be part of eosinophilic gastroenteritis</p>	<p>Estimated prevalence of 6.3 per 100,000 in the US [36]</p>	
<p>Eosinophilic gastroenteritis (EGE; also known as eosinophilic enteritis)</p> <p>Eosinophilic gastroenteritis is a rare digestive disease characterised by eosinophilic infiltration into segments of the intestinal tract. Symptoms include abdominal pain, diarrhoea, nausea, vomiting, bloating, or ascites. The aetiology remains unknown, but there is some evidence to support the role of allergens in the pathogenesis of this disorder</p>	<p>Estimated prevalence is 8.4 per 100,000 in the US, although this is likely an underestimate as misdiagnosis is common for these conditions [36]</p>	
<p>Eosinophilic granulomatosis with polyangiitis (EGPA)</p>		

Table 1 continued

Disease information	Estimated prevalence	Guidelines
<p>EGPA is a rare, chronic autoimmune multisystem disease that is associated with high levels of eosinophilic inflammation of various tissues, as well as small- to medium-sized blood vessels, resulting in damage to multiple organs, including lungs, skin, heart, gastrointestinal tract, and nerves. Diagnosing the condition is challenging given its rarity and the varied clinical manifestations of the disease, which can be difficult to distinguish from severe eosinophilic asthma, hypereosinophilic syndrome (HES) with asthma, and chronic eosinophilic pneumonia</p>	<p>The estimated global and European prevalences are 15.27 and 12.13 cases per million individuals, respectively [14]</p>	
Eosinophilic pneumonia		
<p>Eosinophilic pneumonia comprises a group of lung diseases in which eosinophils appear in increased numbers in the lungs and usually in the bloodstream, with symptoms that range from mild to life-threatening, including shortness of breath, fever, chest pain, cough, wheeze, and decreased levels of oxygen in the blood. In acute eosinophilic pneumonia (AEP), the number of blood eosinophils may be normal, while chronic eosinophilic pneumonia (CEP) generally shows high numbers</p>	<p>AEP: 9.1 per 100,000 patient-years; CEP 0.23 per 100,000 population [56]</p>	
Hypereosinophilic syndrome (HES)		
<p>A heterogenous group of rare disorders characterised by high numbers of eosinophils in blood and tissues, which can cause progressive damage to any organ and, if left untreated, be fatal. HES most commonly impacts the skin, heart, lungs, gastrointestinal tract, and nervous system</p>	<p>0.15–0.89 per 100,000 persons in the UK [57]</p>	<p>British Society of Haematology Guidelines for the Investigation and Management of Eosinophilia</p>
Nasal polyposis (NP)		

Table 1 continued

Disease information	Estimated prevalence	Guidelines
Nasal polyps are growths on the lining of the sinuses and nasal passages. In patients with nasal polyps, elevated levels of eosinophils accumulate in the upper respiratory tract, which can lead to breathing problems, frequent sinus infections, or loss of the ability to smell. Nasal polyps are also associated with EA	Estimated prevalence of 10.9% in Europe and 11.9% in the US [58]	British Society for Allergy and Clinical Immunology (BSACI) Guidance for the Management of Patients with Rhinosinusitis and Nasal Polyposis

^aDiseases in the table are listed in alphabetical order and do not reflect disease prevalence or relative involvement of eosinophils in these conditions

can be collectively referred to as eosinophil-associated diseases (EADs) [6, 7].

Many people are living with EADs worldwide; this collection of diseases includes common illnesses such as eosinophilic asthma [8, 9], less common eosinophilic gastrointestinal diseases (EGIDs), and rare conditions, such as eosinophilic granulomatosis with polyangiitis (EGPA) [10, 11] and hypereosinophilic syndromes (HES) [2]. People with EADs often face a substantial disease burden, poor health outcomes, and a poor health-related quality of life (HRQoL), which affects both the patient and their support network (e.g. family, friends, caretakers, and colleagues) [4, 12–14]. This burden is due to the severity of their illness [13, 15, 16] and a range of healthcare barriers, including delayed times to referral, diagnosis, and treatment, among others [12, 17, 18]. Furthermore, their lives are often disrupted by debilitating symptoms, associated flare-ups, and comorbid EAD-associated conditions that require regular visits to the emergency department, hospital admissions, and a ‘cycling’ between multiple healthcare professionals (HCPs) [6, 13, 15, 19].

In many instances, these patient barriers and challenges stem from poor recognition of EADs by HCPs [12, 14, 20–22], which often leads to delays in receiving an accurate diagnosis, accessing specialist care, and receiving effective and safe treatments for the condition [12, 13, 19]. People with EADs often rely on long-term or intermittent oral corticosteroids

(OCS), sometimes administered through multiple routes and in addition to other therapies, to suppress inflammatory activity and control their symptoms and disease flares [12, 13, 21]. Unfortunately, many commonly used treatments do not specifically target eosinophils despite these cells being a critical part of the underlying biological cause [6, 7]. Personalised treatment and earlier implementation of targeted safer anti-inflammatory treatment options, such as the new generation of eosinophil-targeting biologic therapies, may improve patient outcomes and could potentially avoid the adverse effects associated with OCS use [23–27]. As EAD biology and EAD patient needs become better understood among the scientific and healthcare communities and newer, innovative therapies become more widely available, there is a huge opportunity to improve patient outcomes [6, 7].

In 2018, a group of representatives from patient support groups, professional organisations, and the academic asthma treatment community developed a Patient Charter, which set forth six principles for the care of patients with severe asthma. That Charter outlined key patient expectations for management of their condition and described a basic standard of care for severe asthma according to the latest science and best practice understanding [28]. The 2018 Patient Charter was subsequently used as a guide by the Task Force to Improve Access to Better Care, when they developed the 2020 Global Quality Standard for managing severe

asthma. As a complement to the 2018 Patient Charter, the 2020 Global Quality Standard was designed as both a guide and a stimulus for key stakeholders (e.g. governments, payers, policy-makers) to instigate changes that improve early identification and diagnosis of severe asthma, prioritise timely referral to specialists, and optimise treatment and ongoing management [17]. Together, the 2018 Charter and the 2020 Quality Standard have provided a roadmap to clinically meaningful improvements in multiple aspects of care for patients with severe asthma [17, 28]. For example, since 2018, a cumulative OCS threshold of 1 g has been established in the literature and recommendations from the Global Initiative for Asthma (GINA) now reflect the adverse effects of OCS and suggest that, whenever possible, OCS should be avoided in managing asthma [29].

These two articles have highlighted how efforts to improve long-term patient outcomes must synergise the work of HCPs, health systems, policymakers, patient communities, and patient advocacy groups to optimise multiple aspects of care and treatment, including improved EAD diagnoses and timely access to specialist care. Furthermore, those efforts have been complemented by two recently established expert consensus definitions for clinical remission in asthma and severe asthma treatment super-response [30, 31]. These consensus definitions—both of which consist of generally similar criteria and describe roughly the same notion of disease remission in asthma—represent a defining moment in asthma management, and hopefully in the treatment of EADs in general, as they make it possible for clinicians to address important questions about treatment standards and improved disease management/awareness, with remission as the ultimate treatment goal.

An example of the progress that can result from consensus groups and use of the Delphi

approach occurred in the late 1980s with the Rome group. The Rome group was established to answer difficult questions about a group of gastrointestinal disorders through the Delphi approach. This group ultimately developed the first diagnostic guidelines for irritable bowel syndrome in 1989 and it was the starting point for consensus-based criteria that have subsequently been established for a multitude of functional gastrointestinal diseases [32, 33]. Indeed, as the Rome group was very successful in making progress in gastrointestinal disease, our hope is that the recent progress in the field of severe asthma can become the foundation for the formation of an international working group with a common steering committee that can oversee disease specific sub-committees to drive, develop, and implement focused treatment recommendations for individual EADs. This article is based on principles that were debated and refined over a series of virtual discussions and does not contain any new studies with human participants or animals performed by any of the authors.

CHARTER PURPOSE

To support this call to action, we—a group of leading patient advocacy groups and treating clinicians—present this charter to (1) outline key rights that we fervently believe patients should expect from the management of their condition(s) and (2) set out a basic standard of care to improve health outcomes for people affected by these life-altering and sometimes fatal diseases. It aims to unite the clinical community with the advocacy communities, which support people with EADs, by setting out clear actions that can improve patient care. This charter has been developed in line with the latest science and best practice understanding. It aims to inspire policymakers and healthcare decision-makers around the world to act to

reform healthcare practices for people with EADs.

What Do All Individuals with EADs Deserve from Their Care?

Principle 1: People with EADs, Their Caretakers, HCPs, and the Public Must Have Greater Awareness and Education about EADs

Degrees of EAD awareness vary among HCPs, payers, and patients. This is due to the rarity of some of these conditions and the highly specialised and complex nature of EADs, including their heterogeneous clinical presentation, which can drive patients to visit multiple different clinical subspecialty providers who may not understand the potential impacts of the condition on other organ systems [34]. Furthermore, those in these groups, including HCPs, payers, and patients, frequently lack an understanding that eosinophils contribute to many aspects of these disorders (e.g. eosinophil immune dysfunction) and their effects on patients, healthcare systems, and HCPs across myriad clinical specialties [12].

Global professional societies for clinical subspecialties involved in EAD care and treatment, as well as guidelines for EAD clinical management, do exist for some conditions; however, expertise and guidance are not always used in regional or national approaches to disease management [19, 20, 35]. Furthermore, given that some clinical subspecialties are further divided into multiple specialised subdivisions, it can be challenging to find specialists who are knowledgeable about specific EADs. Since 2008, important steps have been taken to identify and define subsets of EADs by classifying the specific conditions, including the introduction of the first International Classification of Disease (ICD) codes for several EADs, including eosinophilic gastritis (EG; 535.70, now K52.81 in ICD-10), eosinophilic

gastroenteritis (558.41, now K52.81 in ICD-10), and eosinophilic colitis (558.42, now K52.82 in ICD-10) [36, 37]. As of 2020, additional ICD codes for other subsets of EADs (eosinophilic esophagitis, ICD-10 code: K20.0) have been introduced thanks to collaborative efforts between patient associations and expert clinicians [37].

Targeted, tailored education and awareness programmes are necessary for HCPs in both primary and secondary care to enable a timely diagnosis and access to appropriate care. For primary care, educational programmes should emphasise conditions that may be driven by eosinophils; they should also describe symptoms and/or laboratory findings that may be associated with persistent eosinophilia and disease manifestations, some of which may not correlate with symptoms (e.g. elevated liver enzymes or occult cardiac involvement, which is suspected based on elevated troponin in the total absence of symptoms) and which may indicate the need for referral to appropriate specialists who can more conclusively diagnose and properly treat the disease [6, 7]. For HCPs in secondary care, messages should focus on providing an accurate diagnosis, using modern diagnostic tools, consulting with other subspecialties to evaluate other involved organ systems, and considering steroid-sparing treatment options, which may enable a more targeted approach to treating the underlying EAD [7, 20, 21, 38]. Where clinical guidelines currently exist, national HCP groups must support increased awareness and adoption of these guidelines into national best practices. Furthermore, these efforts should be supported by appropriate funding for education and skills development to ensure continued medical education for all HCPs involved with the diagnosis, treatment, and long-term management of people with EADs. This medical education should be introduced across a range of

specialities, including haematology, allergy, pulmonary, cardiology, gastroenterology, and primary care, where patients with EADs commonly enter the healthcare system.

Currently, little patient guidance exists about where to find and access educational materials and other helpful resources after diagnosis of an EAD. As such, better provision of accurate and relevant information is necessary to support people with EADs to manage their conditions. For example, it is critical to empower patients and their support network with sufficient resources to make the best use of appointments with their clinicians so that they can play an active and informed role in treatment decisions and management of their condition [38]. For EADs, this informed decision-making requires a basic understanding of how EAD is involved in the pathology of their specific condition. Comprehensive educational resources and tools need to be updated as our understanding of EADs evolves and should be made readily accessible to people with presumptive or newly diagnosed EADs.

While these should offer baseline, foundational information on the role of eosinophils across the broad range of all EADs, EAD-specific materials reflecting unique patient challenges for the different illnesses (e.g. the impact of diet in gastrointestinal EADs), diagnostic processes, and potential treatments for each disease must also be accessible. These resources should be made available through their HCPs or delivered through better use of targeted digital and social campaigns to reach specific audiences, utilising best practices from other disease areas. Moreover, search engine optimisation should also be considered to ensure digital sources of information are easily accessible to patients.

In addition to the optimised delivery of educational resources described above, patient advocacy groups will continue to be a critical

resource for patients and their support network [37, 39, 40]. Coupled with these improvements in HCP and patient education, we recognise that there is also a need for wider public awareness about the prevalence and burden of EADs, especially with respect to their impacts on patient HRQoL. Greater public awareness about EADs will help patients and providers recognise symptoms that warrant further evaluation, thereby reducing underdiagnosis, time to diagnosis, and the social and professional withdrawal that is common with certain EADs, which will drive further improvements in patient care. Indeed, increased public awareness of EADs will also improve the success of attempts by patient advocacy groups and others to obtain better financial coverage for long-term treatment and care of these conditions.

Principle 2: People with EADs Must Receive a Timely, Accurate Diagnosis

A prompt, accurate diagnosis is the foundation of effective care. Unfortunately, the patient journey from the onset of symptoms to EAD diagnosis can take many years, depending on the specific disease [41]. Patient surveys in EGIDs have shown that some patients received a diagnosis late in life, although the time varies depending on the specific EGID [19]. In terms of EADs in general, an initial diagnosis may occur in primary care (e.g. for conditions such as atopic dermatitis or asthma) [42]; however, given the often rare and complex nature of certain EADs, a formal diagnosis usually requires more in-depth assessments (e.g. imaging, bronchoscopy, or endoscopy with biopsies) after referral to a specialist [34]. Indeed, due to poor EAD recognition, patients with these conditions may not seek care, and when they do, they are frequently referred to several HCPs, leading to significant delays in accessing the specialist care they require [16, 19].

Case study: an arduous journey to diagnose EG and/or eosinophilic duodenitis (EoD)

Limited disease awareness and a general lack of diagnostic guidelines mean that people with eosinophilic gastritis and/or eosinophilic duodenitis (EG/EoD) often face substantial delays in receiving an accurate diagnosis for their condition. In theory, diagnosis of EG/EoD should be relatively straightforward, requiring a detailed clinical history and quantification of eosinophil levels in the blood and tissue.

In practice, however, the path to receive an EG/EoD diagnosis is often challenging. Indeed, a recent study reported the average time from the first symptom to diagnosis was **more than 3.5 years**, although it is noteworthy that this average does not account for the large number of patients who were undiagnosed or misdiagnosed, which would increase this delay [19].

A number of common challenges lead to a failure to diagnose EG/EoD accurately, such as the following:

1. Common symptoms of EG/EoD include abdominal pain, diarrhoea, and early satiety, which may overlap with other gastrointestinal conditions. Thus, people are often misdiagnosed with irritable bowel syndrome, functional dyspepsia, or even food intolerance. In the study described above, **38.2% of patients were misdiagnosed**.
2. People with EG/EoD can be shuffled between multiple HCPs, some of whom may lack experience with treating EG/EoD. In the study described above, on average, patients visited **7.2 distinct clinicians**, including more than 2 gastroenterologists.
3. Patients with EG/EoD often undergo several different invasive procedures. Certain procedures are performed to aid diagnosis, some of which must be repeated for additional sampling, while in other cases, the procedures are unnecessary because they are the wrong investigation. Reports indicate that diagnostic procedures can include multiple esophagogastroduodenoscopies, colonoscopies, abdominal imaging, and stool analyses, not all of which are necessary to diagnose EG/EoD. This panel of tests can take more than 2 years to perform, and even when biopsies are conducted for confirmation, they may not show adequate tissue eosinophilia (a key criterion for providing an accurate diagnosis) due to sampling error, nonstandardised pathology reporting, or when infiltrates present deep within the tissue beyond what is accessible with routine biopsies.

In short, developing a standardised guideline for EG/EoD diagnosis and better educational tools could significantly improve recognition, as well as the time to and accuracy of diagnosis.

Patients who present to primary care physicians with clinical features consistent with an EAD should receive a basic workup, including a blood eosinophil count (appreciating that it is not always elevated in many EADs, including severe asthma and eosinophilic esophagitis, among others), and should be referred to a relevant specialist if the clinical picture is consistent with an EAD. Since consideration of an EAD in the differential diagnosis is critical to standardising this basic workup, greater awareness and targeted education are needed for HCPs about the conditions that are driven

primarily by eosinophilic inflammation (see Principle 1). Clear referral guidelines, referral criteria, and the identification of recognised experts in different countries with access to clear and up-to-date diagnostic modalities and treatment options are also necessary to enable timely and appropriate referrals [19]. This is particularly important for gastrointestinal EADs where, aside from HES with gastrointestinal involvement and eosinophilic esophagitis (EoE), diagnostic criteria are not well established. These standards should be coupled with appropriate patient screener questionnaires to assist in establishing an accurate diagnosis, as

people with EADs may not always report the full burden of their condition or may not be aware of the potential symptoms associated with elevated eosinophil counts. Moreover, efforts to develop less invasive means of diagnosing and following disease activity in EADs should be a priority, as this would improve the time to and accuracy of diagnoses while reducing patient burden (e.g. repeated invasive procedures).

Many other conditions have clearly defined “waiting time targets” to ensure rapid diagnosis and treatment. Establishing similar targets and referral pathways for EADs would enable patients to receive a more timely, accurate diagnosis. Indeed, streamlining the patient journey is key to improving long-term outcomes and HRQoL for patients with EADs [38].

Principle 3: All People with EADs Must Have Access to an Appropriate Multidisciplinary Team, When Necessary

The diagnosis, management, and treatment of many EADs, including severe eosinophilic asthma, HES, EoE, and EGPA, require input from a multidisciplinary team (MDT) to confirm the diagnosis and determine the best treatment approach on a case-by-case basis [12, 20, 21].

availability, and geography [12, 13, 19]. Given the rarity of some of these conditions, expertise is often lacking in certain regions, which can mean patients either go without appropriate care or must travel long distances to access specialists. These drawbacks may influence patients’ decisions about treatment choices given the potential costs, including time away from work, school, or family responsibilities. Patients with EADs may also experience physical limitations because of their symptoms, which can prevent them from being too far from home for extended periods of time. Additionally, in countries with insurance-based healthcare systems, like the US, patients with EADs may not be able to access specialist care if they are uninsured or their insurance does not cover the visit [12].

In addition to the above barriers against access to appropriate care, patients with EADs may have more than one EAD, additional comorbidities, and/or complex, multisystem expression of a single EAD (e.g. EGPA or HES), and they may often see multiple clinicians who treat each disease or clinical manifestation independently, rather than providing the holistic approach that is frequently needed

Case study: dietary therapy for EoE

While dietary therapy may not be appropriate for treating all EADs, with EoE, which is, in part, a food antigen-mediated disease, dietary therapy can often help to induce clinical and histological remission [43].

Dietary therapy eliminates the food antigens most commonly reported to cause oesophageal eosinophilia and food allergies, including milk, eggs, wheat/grains, legumes (which include soybeans and peanuts), tree nuts, fish, and shellfish. While elimination diets are often effective treatments for EoE, the dropout and nonadherence rate is high amongst adults (38%), potentially reflecting the psychosocial and financial challenges dietary therapy poses, including the high number of endoscopies they will need to undergo to steer the diet, which in turn may impair health-related quality of life.

Patient access to appropriate treatment must be improved for all EADs, which includes dietary therapy in EoE that should be managed by a multidisciplinary team with knowledge of eosinophilic gastrointestinal disorders and the essential specialized dietetic support.

Many barriers can limit patient access to appropriate specialist care, including socioeconomic status, language, education, care

[13, 36, 44]. This lack of coordinated care can create an inadequate and siloed treatment approach that fails to achieve the best possible

outcomes for the patient. It also exacerbates the geographic challenges in many cases: a patient with both severe eosinophilic asthma and EoE may need to see a pulmonologist in one location hours from their home and a gastroenterologist similarly far away on a different day and time.

We recommend that people with EADs be managed by multidisciplinary teams (MDTs) with access to appropriate resources and personnel [38]. For instance, in oncology, the MDT approach emerged in the mid-1980s and has been shown to result in better treatment adherence and tolerance, reduction in long-term side effects of treatments, improved quality of life, and, ultimately, improved outcomes and survival [45]. Access to comprehensive MDTs for patients with other conditions, including EADs, has been lacking. This care planning should include an EAD coordinator (e.g. a nurse specialist), with an understanding of all of the relevant disciplines and HCPs trained in the EAD spectrum, who can bring together the relevant specialisms required to treat a person with an EAD. As a dedicated EAD coordinator can be costly, financial support must be provided to cover the costs of this resource, which can ultimately reduce health-care burden/costs and improve patient outcomes. Expert care centres with these resources should be identified and validated at the regional and national levels. Circumstances will differ from patient to patient, so care must be personalised to focus on each individual's priorities, which can be accomplished by using a shared decision-making model [38].

New models of care are needed to make better use of regional expertise and reduce the geographic, travel-related, and socioeconomic barriers that sometimes prevent access to care. This can be achieved through better use of technology, such as telemedicine/video consultations, disease management smartphone apps, and new home diagnostic kits or biomarker monitoring. These initiatives have the potential to increase access to specialist MDTs and, in many cases, eliminate the need for travel [38]. Local leadership should be established to champion improved care for people with EADs. Such leadership could come from HCPs

or health system leaders, who would be responsible for ensuring care standards are maintained.

Coupled with the recommendations above, accessible and readily available information is necessary to help patients and their support network find specialist care. This is an area where patient advocacy groups can help patients identify and connect with specialist MDTs. An online specialist care finder, like the global care finders provided by the American Partnership for Eosinophilic Disorders (APFED) and EOS Network, could be made available on public health agency websites or patient advocacy group websites in each country to make this connection possible [46, 47].

Principle 4: People with EADs Must Have Access to Safe and Effective Treatment Options Without Unnecessary Regulatory Delays

Poor understanding of the central role of eosinophilic inflammation in many of the EADs can result in suboptimal treatment choices and excessive OCS use [13, 21]. Patients are often reliant on OCS or even multiple-use OCS in those with comorbid EADs, which are associated with life-altering acute and chronic adverse effects [23, 25, 27]. Despite the advent of targeted, biological therapies, access to these new therapies can be limited, and a 'fail-first' approach to treatment can make these innovative treatments inaccessible to patients in a timely manner. Moreover, a lack of payer knowledge about the burden of EADs, the latest evidence, the latest studies, and the acceptance of smaller trials and data sets limits their understanding of these conditions and thus their motivation and willingness to assess innovative medicines properly. In some cases, patients may turn to self-management of their conditions to alleviate their symptoms, often through lifestyle modifications and restricted diets and sometimes through self-medication, which may include inappropriate and potentially dangerous self-adjustments to OCS dosing.

The approach to the treatment of EADs across and within countries is not always consistent; even for more common EADs, such as eosinophilic asthma, a failure to measure and

recognise an elevated blood eosinophil count can limit the appropriate treatment options available to patients [48]. Inexpensive, noninvasive diagnostic tools and disease biomarkers, such as the blood eosinophil count and exhaled nitric oxide testing (FeNO) for severe eosinophilic asthma, along with more invasive tests including tissue biopsies, should be readily available to diagnose and identify the most appropriate treatment for people with EADs.

Robust global treatment guidelines need to be developed or updated to reflect new treatment options, which address the underlying mechanisms of disease and ensure patients are offered the right treatment, at the right time, with the fewest possible adverse effects. Specifically, efforts should be taken to reduce and avoid the use of OCS when safe and effective alternatives are available. People with EADs should also receive regular treatment evaluations to ensure their conditions are managed appropriately and treatment is optimised. These evaluations could be accomplished through innovative methods that have become more mainstream due to the COVID-19 (coronavirus disease) pandemic, such as, for example, better use of telemedicine [49]. Updated guidelines should also be shared widely amongst HCPs involved with the treatment of people with EADs to ensure consistent and coordinated care.

Patients should also receive relevant information about their EAD from their HCP and healthcare system and/or through patient advocacy groups. This information should be in a simple and clear format to support increased understanding of the roles of eosinophils as a critical component of inflammation in EADs, as well as the treatment and management options available to support shared decision-making [38]. All patients with an EAD should have a dedicated 'action plan' to help with the self-management of their condition. Such plans should be developed in partnership with their MDT and based on up-to-date information from relevant resources (such as EAD-specific patient advocacy groups) and in coordination with family and loved ones who support their patient journey.

CONCLUSION

EADs place a significant burden on the lives of millions of people worldwide with these diseases, as well as on their healthcare systems. A number of clear steps can be taken to help reduce this burden and improve patient outcomes. Unfortunately, the rarity of some of these conditions means EADs are often poorly understood and suboptimally treated. Even for the more common conditions like asthma and atopic dermatitis, management guidelines are infrequently followed in clinical practice. As evidenced by progress that was made across multiple functional gastrointestinal disorders over nearly 3 decades by the Rome group, and much more recently in the field of severe asthma, to optimise patient care we must establish disease-specific, best practice recommendations and review or revise current care practices for the diagnosis and management of all EADs [17, 28, 30–33]. This includes engaging stakeholders at multiple levels of healthcare systems (e.g. HCPs, policymakers, payers, patient communities, patient advocacy groups) and experts at both national and international levels. Furthermore, there is an urgent need for increased recognition and understanding of EADs and the role of eosinophilic inflammation in EAD pathogenesis. Such initiatives will better support people with EADs to receive accurate, timely diagnoses and enable them to access state-of-the-art care and treatment in an appropriate setting; indeed, they will also lead to further development of other new therapies that are tailored to each patient's condition/phenotype (i.e. personalised medicine).

The principles we have set out in the charter demonstrate the core elements of quality care that people with EADs must receive. We urge healthcare providers, health systems, and policymakers around the world to swiftly implement these principles and ensure that the current advancements and latest approaches in science reach the patients who need them most.

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