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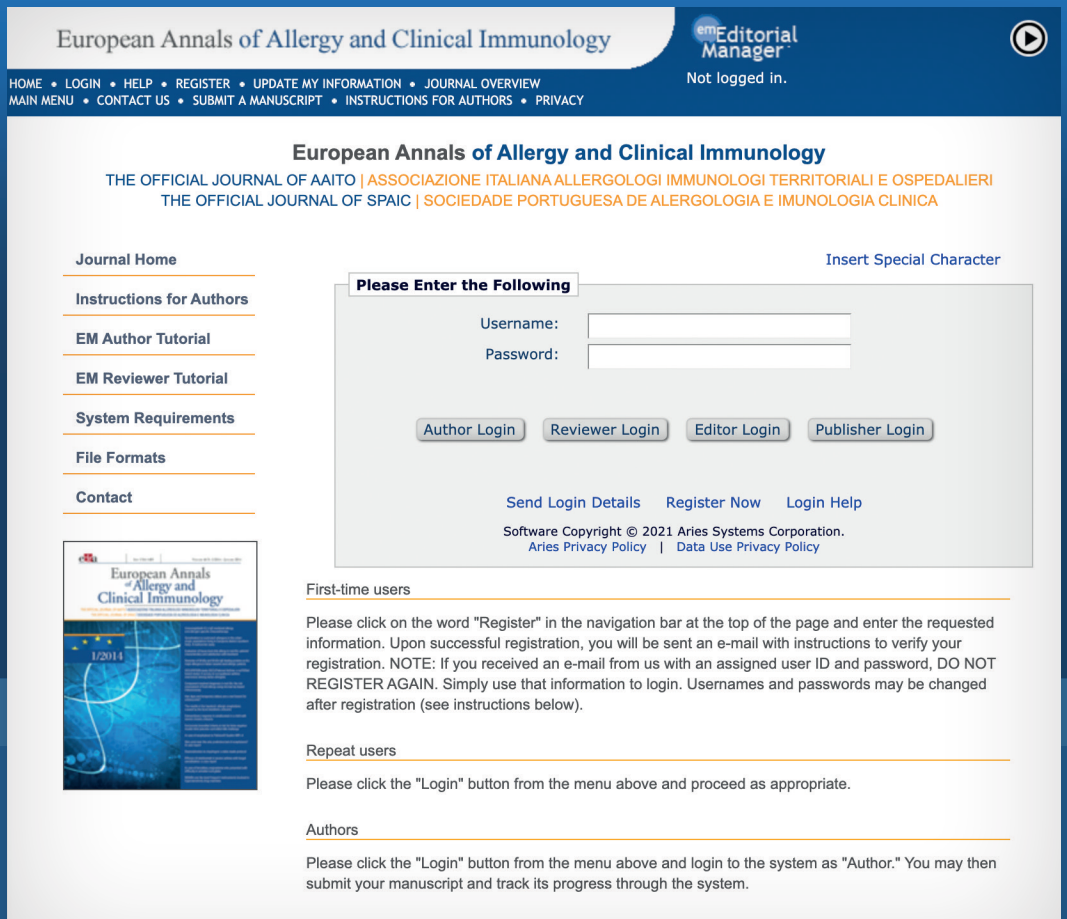
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edra REVIEW | Eur Ann Allergy Clin Immunol | Vol 56, N.5, 195-209, 2024

Alessandro Maria Marra[1], Carlo Maria Rossi[2,3], Mario Andrea Piga[4], Gianluca Moroncini[4,5,6], Maria Beatrice Bilò[6,7]

Eosinophil-associated diseases: the allergist's and clinical immunologist's perspective

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Key words

Eosinophilia; hypereosinophilia; eosinophilic disorders of gastrointestinal tract (EGID); eosinophilic granulomatosis with polyangiitis (EGPA); hypereosinophilic syndrome (HES).

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Impact statement

Eosinophilic disorders encompass a broad range of heterogeneous conditions. Allergists and clinical immunologists have a deep knowledge of type 2-eosinophilic inflammation. They can better refine the eosinophilia workup and make the most appropriate diagnosis.

Summary

Eosinophil-associated diseases (EADs) refer to heterogeneous conditions in which eosinophils are believed to play critical pathological roles. They encompass common respiratory conditions, such as asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), less common primary eosinophilic disorders of gastrointestinal tract, and rare conditions including eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES). A literature search was carried out in January 2024 in the MEDLINE and Scopus databases using the PubMed search engine (PubMed, National Library of Medicine, Bethesda, MD). A diagnostic workup is proposed. From allergist's point of view, we focused the review on 4 groups of eosinophilic disorders of specific interest. Our increased understanding of type 2 inflammation and biology has recently led to development of highly effective precision targeted therapies that are now approved for a growing number of eosinophilic disorders. Novel targeted biologics have a major impact on treatment strategies and have resulted in major advances in our understanding of the pathogenesis of these disorders. In the context of EADs, according to the heterogeneity of eosinophilic disorders, a multidisciplinary approach should be adopted. Allergists and clinical immunologists play an important role as they have a clear understanding of the eosinophilic inflammation and the role of cytokines and are trained to recognize and characterize type 2 (T2) inflammation and its associated pathologies.

Introduction

Over the past two decades, it was discovered that a range of inflammatory diseases involving several organ systems with elevated eosinophil counts in blood and/or tissue was primarily driven by abnormal regulation of the number and activation state of eosinophils. Eosinophil-associated diseases (EADs) refer to these heterogeneous conditions in which eosinophils are believed to play critical patho-

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logical roles (1). EADs encompass common respiratory conditions such as asthma, (mostly eosinophilic) chronic rhinosinusitis with nasal polyps (CRSwNP), less common eosinophilic disorders of the gastrointestinal tract (EGID), and rare conditions including eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES) (2). Despite remarkable progress in understanding pathophysiologic mechanisms of eosinophilic disorders, gaps remain in this very heterogeneous group of diseases. While common EADs are well-characterized, others are extremely rare conditions and have very heterogeneous clinical presentations. The awareness of EADs varies among healthcare professionals. Therefore, patients with EADs face substantial disease burdens due to the severity of their illness and associated disease flares, and a range of healthcare barriers, including delayed times to referral, diagnosis, and treatment, often involving repeated visits to multiple clinical subspecialties (3), therefore, a multidisciplinary approach should be adopted. In the context of a multidisciplinary team, allergists and clinical immunologists play an important role. Indeed, their deep knowledge of type 2 (T2)-eosinophilic inflammation allows them to have an holistic view of hypereosinophilic disorders. They are trained to recognize and characterize type 2 inflammation and its associated pathologies (**figure 1**). The aim of this review is to highlight the state of the art regarding the knowledge of blood eosinophilia and hypereosinophilia (proposing a diagnostic workup) and the most important eosinophil-associated diseases focusing particularly on those where significant advancements have been made in targeted therapy towards type 2 inflammation in recent years.

Methods

A literature search was carried out in January 2024 in the MEDLINE and Scopus databases using the PubMed search engine (PubMed, National Library of Medicine, Bethesda, MD). Keywords in the query included: "Eosinophilia, hypereosinophilia eosinophilic disorders of gastrointestinal tract (EGID), eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome (HES)". The first search was limited to articles published over the last fifteen years. Some older papers of particular interest were subsequently included. A narrative review was performed based on the relevant literature, including original articles and reviews of interests. The reference lists of all articles were scanned for references not identified in the initial research. We favored papers with the most updated data regarding the incidence, prevalence of diseases and new therapeutic perspectives targeting type 2 inflammation. Regarding blood eosinophilia, we searched the literature to propose a diagnostic workup for persistent unexplained eosinophilia or hypereosinophilia to assist clinicians in directing and diagnosing any related pathologies more effectively. The research was performed exclusively by allergists and clinical immunologists to consider their role as profound experts and guides for other specialists in the study of blood eosinophilia and type 2 inflammation. From allergist's point of view, we focused on 4 groups of eosinophilic disorders of specific interest which are characterized by eosinophilic and type 2 inflammation: eosinophilic asthma and CRSwP, eosinophilic disorders of the gastrointestinal tract (EGID), EGPA end HES.

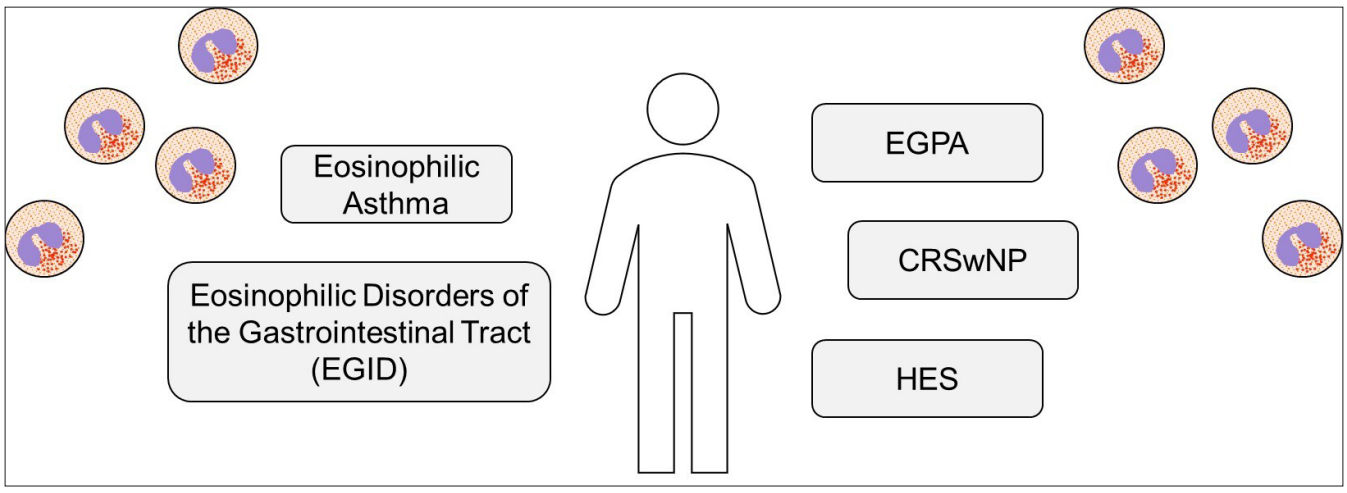
Results

106 papers were selected, included and cited. Starting from the literature, we examined the diagnostic workup of blood eosinophilia and hypereosinophilia and subsequently the spectrum of eosinophilic disorders of interest.

Diagnostic workup of eosinophilia

Peripheral blood eosinophilia can occur as absolute blood eosinophilia (> 0.5 × 10^9/L), relative blood eosinophilia (> 6% in

Figure 1 *- The spectrum of eosinophilic diseases: allergist's point of view.*

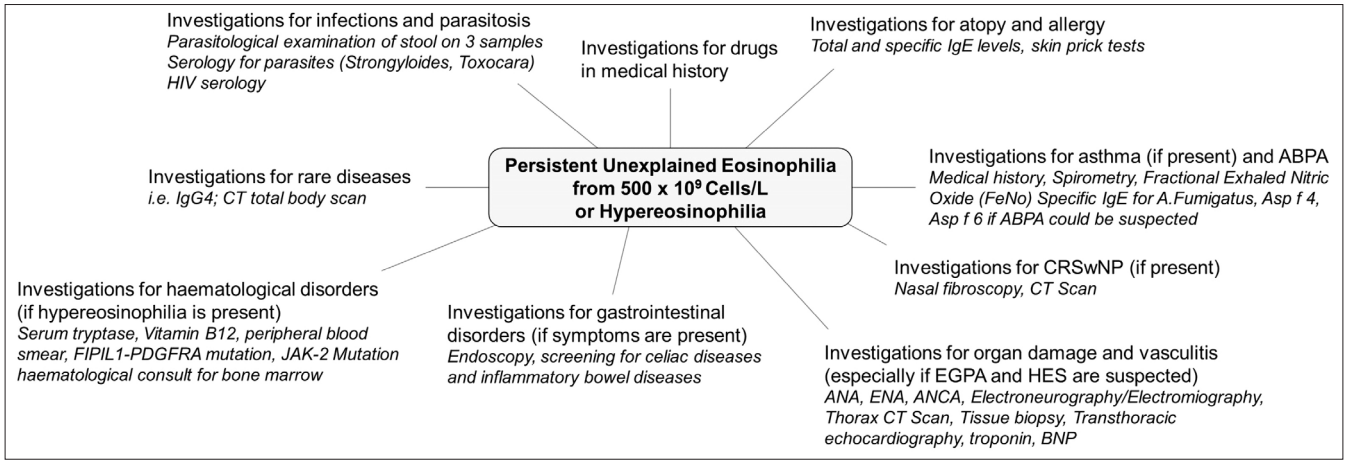


differential counts) or combined absolute and relative eosinophilia (absolute > 0.5 × 10^9/L and > 6%). Absolute peripheral blood eosinophilia can be classified into mild eosinophilia (0.5-1.49 × 10^9/L), moderate hypereosinophilia (1.5-5.0 × 10^9/L), and severe hypereosinophilia (> 5.0 × 10^9/L) (4). In the original definition of hypereosinophilia (HE), "persistent" was defined as absolute eosinophil count (AEC) > 1.5 × 10^9/L for at least 4 weeks (5). The World Health Organization (WHO) recently also confirmed a 4-week interval as reasonable observation period (6). However, during the Year 2021 Working Conference, this interval was once again debated. Many authors agreed that the term "persistent" should apply to HE recorded on at least 2 occasions with a minimum "time-interval" of 2 weeks (4). The diagnostic approach to a wide range of eosinophilic syndromes is facilitated by the well-established division into primary and secondary (reactive) eosinophilic states (7) (**table I**) which have been further refined according to updated classifications (8, 9). Not only HE but also eosinophilia can be related to systemic diseases: recent ACR/EULAR 2022 criteria for ANCA-associated vasculitides include for diagnosis of EGPA a minimum eosinophil count ≥1 × 10^9/liter (10). Recently, new refined diagnostic criteria and classification of primary eosinophil disorders was proposed (4, 11) (**table I**). Virtually any organ system may be susceptible to the effects of sustained eosinophilia but is very important to classify eosinophilia into the right diagnostic path, dividing the primary causes from the secondary causes. Secondary eosinophilia has numerous causes that may require diagnostic evaluation by a lot of sub-specialty consultants. In developing countries, eosinophilia most commonly derives from infections, particularly tissue-invasive parasites (12). Allergy/atopy and hypersensitivity conditions, drug reactions (for instance drug eruption with systemic symptoms – DRESS – Syndrome), collagen-vascular disease and vasculitides like eosinophilic granulomatosis with polyangiitis (EGPA) granulomatosis with polyangiitis, systemic lupus erythematosus, pulmonary eosinophilic diseases like idiopathic acute or chronic eosinophilic pneumonia or allergic bronchopulmonary aspergillosis (ABPA), allergic gastroenteritis (with associated peripheral eosinophilia), and metabolic conditions such as adrenal insufficiency are diagnostic considerations in the appropriate clinical context (13-15). Eosinophilic disorders are numerous and have different etiologies, hematological conditions (for example, lymphocytic and myeloproliferative hypereosinophilic syndromes, the latter being characterized by FIP1L1 fusion genes) or conditions that only occasionally present with eosinophilia but can have overlapping features with EGPA (such as HIV infection or IgG4-related disease) should also be considered (16). Non-myeloid malignancies may be associated with secondary eosinophilia that results from the production of cytokines, such as interleukin-3 (IL-3), IL-5, and GM-CSF, which promote eosinophil differentiation and survival. For example, these cytokines may be elaborated from malignant cells in T-cell lymphomas, Hodgkin lymphoma, and acute lymphoblastic leukemias (17, 18). Rare conditions associated with eosinophilia include familial eosinophilia whose genetic basis remains largely unknown (recent association with a CMTM3 mutation) hyper IgE syndrome, Omenn syndrome, episodic angioedema, and eosinophilia (Gleich's syndrome), and eosinophilia-myalgia syndrome (possibly related to tryptophan ingestion or of historical interest, the epidemic of toxic-oil syndrome) (5, 19). Detailed travel history and repeated ova and parasite testing, stool culture, and antibody testing for specific parasites (for example strongyloidiasis) are paramount to identifying infectious etiologies in the appropriate clinical context. Elevated immunoglobulin E levels is a nonspecific finding that is mostly seen in reactive conditions (infectious, allergic "including fungal sensitization/ABPA", vasculitis, and lymphocyte-variant HES), whereas its elevation is variable in patients with clonal disorders (20). Additional laboratory testing can be useful such as troponin T or I, anti-neutrophil antibodies (ANA), anti-neutrophil cytoplasmic

Table I *- Eosinophilia, hypereosinophilia and types of hypereosinophilia.*

Condition	Definition/Features
Blood Eosinophilia	Eosinophil count between 0.5 and 1.5 × 10^9/L eosinophils
Hypereosinophilia (HE)	Eosinophil count > 1.5 × 10^9/L on two occasions one month apart and/or tissue eosinophilia
Hypereosinophilic syndrome (HES)	Blood HE and organ damage or dysfunction caused by tissue eosinophils
Familial (hereditary) hypereosinophilia	Frequently detected in childhood and sometimes associated with immunodeficiencies
Hypereosinophilia of unknown significance	Without familial clustering, underlying pathology, related molecular (genetic) abnormalities or hypereosinophilia-driven organ damage
Primary hypereosinophilia	Driven by clonal neoplastic eosinophils
Secondary (reactive) hypereosinophilia	Non-clonal eosinophilia driven by overproduced cytokines
Possible causes of secondary eosinophilia	Infections, parasites, allergy/atopy, hypersensitivity conditions, drug reactions, EGPA, ABPA, metabolic conditions, hematological conditions, EGID, rare diseases

Figure 2 *- Diagnostic workup of persistent eosinophilia.*



antibodies (ANCA) and imaging tests (chest x-ray, electrocardiogram and echocardiography, and CT scan of the chest, abdomen and pelvis) are suggested by the patient's travel history, presenting symptoms, and findings on physical examination. For eosinophilic lung diseases, pulmonary function testing, bronchoscopy, serologic tests (*e.g.*, *Aspergillus*-specific IgE for diagnosing ABPA) may be obtained to further characterize lung involvement. Endoscopy, gastrointestinal (GI) imaging and fecal calprotectin could be useful for GI symptoms, and at the same time an electromyograph to exclude peripheral neuropathy. The diagnostic workup we propose in case of persistent unexplained eosinophilia or hypereosinophilia is summarized in **figure 2**.

The spectrum of eosinophilic diseases: allergist's point of view

Eosinophils are involved in a wide array of homeostatic processes and pathological diseases. Through the growing understanding of eosinophil physiopathology, it will be possible to better understand the role of eosinophils in disease, and ultimately develop more effective precision therapies. Novel targeted biologics have not only had a major impact on treatment strategies, but also have resulted in major advances in our understanding of the pathogenesis of these disorders. Our increased understanding of type 2 inflammation and biology has recently led to development of highly effective targeted therapies that are now approved for several eosinophilic disorders (21).

Eosinophilic asthma and CRSwNP

Asthma is the most common chronic respiratory illness, affecting about 14% of children and 6% of adults globally with rising prevalence. Severe asthma (SA) affects up to 10% of asthmatic patients and represents a major economic issue worldwide (22). Asthma is characterized by reversible airflow obstruction, airway inflammation and bronchial hyperresponsiveness. Our understanding of asthma as a heterogenous disease with different phenotypes and endotypes has evolved through improved understanding of biologic pathways leading to Type 2 high or Type 2 low inflammation. Over half of asthmatics have type 2 inflammation, characterized by release of IL-4, IL-5 and IL-13 from innate and adaptive immune cells and elevated fractional exhaled nitric oxide (FeNO), serum IgE or blood and sputum eosinophils (21, 23). Type 2 low asthma has been identified by several authors as asthma characterized by increased neutrophils in sputum and/or the absence of type 2 biomarkers. It is mediated by IL-1β, IL-6, and IL-17 (21, 23). Eosinophils have long been recognized as an important element in asthmatic inflammation. This persistent airway inflammation is partly responsible for the high frequency of exacerbations seen in severe eosinophilic asthma. Early studies demonstrated the association of blood and tissue eosinophilia with bronchial asthma, and the relationship between elevated circulating eosinophil count and disease severity (24, 25). Furthermore, blood eosinophil count was identified as a treatable trait and was established as a validated pharmacodynamic and predictive biomarker for response to biologics like mepolizumab or benralizumab in patients with severe eosinophilic asthma (26). Biologics have had significant impact on patients with severe asthma, reducing symptoms and exacerbations, while improving lung function. The treatment decision of which biologic to use is driven by the clinical characteristics of patients and biomarkers even if phenotypes and endotypes often overlap with each other; all biologics have demonstrated variable effectiveness in type 2 inflammation, eosinophil/FeNO/IgE high presentations (27). The anti-IgE monoclonal antibody (omalizumab) is effective in patients with symptomatic allergic asthma who have elevated IgE or directed against perennial allergens (such as dust mites and molds), anti-IL-5/IL-5R agents are more effective in eosinophilic driven asthma.

Dupilumab has broader clinical indications and has been shown to be effective in patients with elevated eosinophils or FeNO; it has been approved for severe asthma patients, even those with oral glucocorticoid dependent asthma (28). Anti-Thymic Stromal LymphoPoietin (TSLP) therapy with tezepelumab, the most recently Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved biologic, reduces asthma exacerbations and improved lung function in patients with blood eosinophils > 300×10^9/L and < 300×10^9/L compared to placebo, suggesting TSLP inhibition may have broader physiological effects, targeting high T2 and low T2 inflammatory pathways, independent of biomarker status (29). The effectiveness of biologic therapies is particularly evident, as observed after one year follow up from the Italian Registry on Severe Asthma (IRSA) in which the positive outcomes were found to be associated to certain factors such as baseline eosinophil count (30). CRSwNP is a chronic inflammatory disease of the nasal mucosa and sinuses that lasts at least 12 weeks with heterogeneous pathophysiology (31), and it is a frequent comorbidity in patients with severe eosinophilic asthma. It is characterized by type 2 inflammation with increased IL-4, IL-5, and IL-13 cytokines that lead to tissue infiltration with eosinophils, lymphocytes, basophils, and mast cells. The development of non-steroid antinflammatory drugs (NSAIDs) exacerbated respiratory disease is often associated and may be mediated by a combination of factors including dysregulation of TSLP-immune response, mast cell activation by an innate type 2 response driven by cysteinyl leukotrienes, and IL-33 (32). IL-5 was implicated in the pathogenesis of nasal polyps (NP) in 1997 when it was found in significant amounts in the NP tissue samples from patients with asthma undergoing polypectomy (33). Neutralization of IL-5 led to a reduction in eosinophilia in the NP tissues (34). But the elimination of eosinophils doesn't improve the symptoms (35). Later, in 2010, IL-5 was found to significantly predict comorbid asthma in patients with NP (36). Clinical symptoms of CRSwNP are nasal blockage, loss of smell (anosmia), nasal discharge, facial pain/pressure, and sneezing because of nasal mucosal thickening and the formation of nasal polyps. Dupilumab was the first FDA and EMA approved biologic for treatment of CRSwNP, followed by omalizumab and mepolizumab (32). All showed improvement in symptoms and imaging and reduced exacerbations. Recent findings from Matucci *et al.* confirm the existence in humans of two phenotypic subsets of circulating and tissue resident eosinophils with differential surface expression of CD62L suggesting that the peripheral blood constitutes the likely source of tissue inflammatory eosinophils with pathogenic activity (37). This implicates that the count of circulating inflammatory eosinophils (iEos) could provide an insight into the inflammatory state of both pulmonary and nasal tissues and eventually become a new biomarker of type 2 inflammation, as IL-5 has been shown to cause CD62L downregulation or shedding (38). Furthermore, circulating levels of iEos might represent a biomarker predictive of clinical response to an anti-IL-5 therapeutic strategy. Both blood eosinophils and iEos are predictive biomarker of efficacy of mepolizumab in severe eosinophil asthma, but both are not predictive biomarkers of efficacy of mepolizumab in concomitant CRSwNP (39). Eosinophilia and T2 inflammation require a comprehensive management approach involving allergists and other specialists from different medical disciplines.

Primary eosinophilic disorders of the gastrointestinal tract

Eosinophilic disorders of the gastrointestinal tract (EGID) are a heterogeneous group of diseases characterized by eosinophilic infiltration and organ dysfunction of the gut which occur in the absence of secondary causes, *i.e.*, drugs, parasitic infections, and vasculitis, such as eosinophilic granulomatosis of polyangiitis (EGPA) or primary hyper-eosinophilic syndromes (40). The interest in EGID has considerably risen in the last years due to the increased awareness of these diseases, the advances in the knowledge of their pathogenesis, and the possibility, for some of them, to treat them with biological therapies which are either approved, such as a monoclonal antibody targeting IL4 and IL13, dupilumab, for eosinophilic esophagitis (EoE) or being evaluated in clinical trials (40, 41). EGID are classified according to the main involved segment of the gastrointestinal tract and include eosinophilic esophagitis (EoE), eosinophilic gastritis, eosinophilic enteritis and eosinophilic colitis, targeting the esophagus, the stomach, the small, and the large bowel respectively (42). When the combined involvement of more than one segment is present, both should be stated separately. Moreover, according to recent nomenclature guidelines, especially with reference to small and large intestine, the precise layer of the gut involved if known, *i.e.,* the mucosa, the muscolaris or the serosa*,* should be specified along with complications when present (42) (**table II**). Among these disorders, EoE is the most frequent and hence the more studied (42). On the other spectrum, eosinophilic colitis (EoC) is the rarest and less known condition among EGID, and its diagnostic histologic criteria pertaining the eosinophil cut-off level are still debated (43). Moreover, EoE is the only disease among EGID being associated with submucosal fibrosis, which is a Th-2 mediated phenomenon. If left untreated fibrosis leads to stenosis and small calliper-esophagus (44). Clinical manifestations vary according to the segment of the gut involved. In adults the major classifying symptom of EoE is troublesome dysphagia with solid foods, particularly meat, with food impaction often requiring endoscopic removal. In children, clinical manifestations of EoE are more heterogeneous and vary with age and include vomiting, regurgitation, abdominal pain dyspepsia, feeding failure to thrive in toddlers and young children, while dysphagia is present in adolescents (40). Eosinophilic gastritis presents with dyspepsia, heartburn, nausea/vomiting and

abdominal pain. Small and large bowel involvement usually is more frequently associated with diarrhea, abdominal pain and weight loss, but constipation and ascites are also described (45). A T helper (Th) 2 pathogenesis has been convincingly ascertained in both human studies and experimental for most cases of EoE, which has been recognized as the last step of progression of the most trajectories of atopic multimorbidity, after eczema, IgE-mediated food allergy, asthma and allergic rhinitis (46-48). The three key elements in the pathogenesis of EoE are epithelial barrier dysfunction, a prominent Th2 inflammatory process, and fibrosis (49). More precisely allergens (both aero and food ones), environmental factors such as pollutants, microbes, an acidic microenvironment are involved as triggers of the disease in predisposed patients, such as those with genetical alterations in epithelial barrier proteins (49). Eosinophils, which are prominent tissue damage mediators in EGID due to their granular proteins appears to be secondarily attracted in the submucosa by other cell types, such as Th2 cells, mast cells and innate lymphoid cells (50, 51). Diagnosis of EGID rests upon both endoscopy and histology. Moreover, they are essential to assess disease activity in response to treatment. Around 90% of patients with EoE present endoscopic abnormalities, including those reflecting inflammation, such as exudates, edema, furrows, mucosal fragility on the endoscope passage, and those reflecting fibrosis and remodeling, such as plaques, strictures, transient or fixed rings and a small-calliper esophagus. The prevalence of these alterations varies with age and disease duration (52). These endoscopic features have been incorporated in a validated grading system for EoE named EREFS, which stands for Exudates, Rings, Edema, Furrows, Stricture, which predicts with high accuracy the diagnosis of EoE in both adults and children (53). Despite its usefulness, endoscopy alone is not sufficient to make a diagnosis and assess disease activity, since in up to a quarter of patients, especially children, no endoscopic abnormalities are found (53). Endoscopic appearance of other EGID is variable and unspecific and include fold thickenings, mucosal erythema, polyps, ulcerations. However, in up to 50% endoscopic exams are normal (54). Besides, mucosal involvement may be absent in case of muscular and serosal disease. Given the patchy distribution of eosinophil infiltrates in EGID, several samples should be collected from different portions of the gut segment involved, usually at least two, and they should be focused on area characterized by mucosal endoscopic alterations (55). When no suggestive features are present at endoscopy, but clinical suspicion is high, biopsies should be randomly collected, in the case of the esophagus from all portions, upper, middle and lower third. Moreover, histological sampling should be performed after every therapeutical intervention, usually after 6 to 12 weeks, to assess response, since clinical manifestations alone are unreliable in predicting disease activity (55). The most important histological feature is the intraepithelial eosinophil infiltrate expressed as the peak number of eosinophils counted in a high-power field (HPF). The diagnostic histological cut-off for eosinophil in the esophagus is 15/HPF and has a high accuracy in discriminating EoE from gastroesophageal reflux disease; it is also used to define histological remission (< 15 eosinophil/HPF) (55). Despite the marked tissue eosinophilia in the gut, serum eosinophilia in EGID is not always present and is usually not a prominent feature (40, 50). Therefore, these disorders should not be ruled out in the presence of normal eosinophil blood counts, and, on the contrary, in the setting of markedly increased eosinophil counts and gastrointestinal symptoms HES with secondary gut involvement should be considered instead. The natural history of EoE has been evaluated in observational studies and in the placebo arm of experimental studies and associated with chronic activity and relentless evolution to fibrosis in the absence of therapy (43). Hence a chronic treatment is generally recommended in EoE according to current guidelines (53, 55, 56). The clinical course of the other non-EoE EGID is still elusive. Indeed, their natural history appears to be more heterogenous, with different possible evolutions, such as persistent remission after one episode, a relapsing-remitting course or persistent activity after the first episode (57). The first line treatment modalities for EoE are protein pump inhibitors, topical swallowed steroids, and allergen-free diets (55, 56, 58, 59). More recently dupilumab have been approved by both the American and European drug regulatory agencies for the treatment of PPI refractory EoE in adults and adolescents aged 12 years or more and who weight more than 40 kilos, although its precise place in the management algorithm is yet to be determined (60-62). Allergen-free diets have a role in the treatment EoE and enable a drug-free treatment. According to Molina-Infante *et al.*, most patients with EoE display one or two food triggers, usually milk and wheat, hence currently food-elimination diets involve at first a reduced number of food categories, usually two, in the so-called two food elimination diet (FED) or 2-FED (63). This "bottom-up approach" is associated with less micro- and macronutrients deficiency and less demanding for the patient as compared to top-down approaches where more categories are eliminated from the beginning. If a clinic-histological response is not obtained after 8-12 weeks, more stringent elimination diets are instituted such as the 4-FED, in which four foods are eliminated including the previous two categories and egg and soy or six foods, including in addition shellfish and nuts (58, 59, 63). Allergy testing has not been found useful in predicting the food triggers in the single patients since they detect an IgE sensitization. However, when prescribing a diet, the concomitant food allergies of the patients should be considered, such as the frequent sensitization/allergy to lipid transfer protein (LTP) or legumes in the Mediterranean area which has been reported in same case series (59, 64). More precisely, sensitization/allergy to the peach LTP, Pru p 3, was reported as a frequent finding in the

Table II *- Epidemiology, clinical and endoscopic features, diagnostic criteria, current therapeutic options in EGID.*

	Eosinophilic esophagitis	**Eosinophilic gastritis/enteritis**	**Eosinophilic colitis**
Epidemiology (Prevalence)	0.5 to 1/1,000 individuals	6.3/100,000 and 8.4/100,000	3.3/100,000 individual
Diagnostic criteria (40, 50)	≥15 Eo/HPF from at least two sites (distal, mid or proximal esophagus)	≥30 Eo/HPF in ≥5 HPF or ≥70 Eo/HPF in ≥3 HPF (stomach) ≥52 Eo/HPF (duodenum) ≥56 Eo/HPF (ileum)	≥100 Eo/HPF (cecum/ascending colon) ≥84 Eo/HPF (transverse/descending colon) ≥ 64 Eo/HPF (sigma/rectum)
Clinical features	Vomiting, epigastric/chest pain, dysphagia, bolus impaction	-Mucosal form: vomiting, abdominal pain, diarrhea malabsorption, protein-losing enteropathy, iron-deficient anemia, failure to thrive (children), melena -Muscolaris layer form[2]: obstructive symptoms, such as dyspepsia -Serosal form[2]: eosinophil-rich ascites	Abdominal pain, diarrhea, weight loss, anorexia
Endoscopic feature	-Linear oriented creases (furrowing) -Strictures -Mucosal rings -Whitish papules -Polyps	Micronodules	-Erythema[#] -Loss of vascularity[#] -Lymphonodular hyperplasia[#]
Histopathological features	Eosinophilic inflammation, eosinophil abscess, eosinophil surface layer, basal zone hyperplasia, dilated intercellular spaces, dyskeratotic epithelial cells, lamina propria fibrosis. Immunostaining for MCP, ECP, IgE, tryptase	Eosinophilic inflammation in different layers Blunt villi Immunostaining for MCP, ECP, IgE, tryptase	Eosinophil cryptitis/crypt abscesses, crypt architectural abnormalities, increased intraepithelial eosinophils, and eosinophils in muscularis mucosa and submucosa Immunostaining for MCP, ECP, IgE, tryptase
Laboratory parameters	Peripheral blood eosinophilia[1]	Peripheral blood eosinophilia[1]	Peripheral blood eosinophilia[1]
Differential diagnoses	Infection HES Neoplasm CTD/SS Small vessel vasculitis Drug reaction	Infection HES Celiac Disease Crohn's disease CTD/SS Small vessel vasculitis Systemic mastocytosis Drug reaction	Infection HES Ulcerative colitis Crohn's disease CTD/SS Small vessel vasculitis Systemic mastocytosis Drug reaction
Association with allergic disorders[&]	+++	++	+
Predominant allergic phenotype	IgE T-cell	IgE T-cell	T-cell
Evolution	Esophageal stenosis if left untreated	Possible disease remission if pediatric onset	Benign course in infants
Therapeutic options	Elemental Diet, 6-, 4-, and 2- FED Topical glucocorticoid Dupilumab	Elemental diets Topical and systemic glucocorticoid	Elemental diet Topical and systemic glucocorticoid

CTD: connective tissue disease; HES: hypereosinophilic syndrome; HPF: high power field; FED: food elimination diet; SS: systemic sclerosis; [1]it is not an universally present feature; [&]it denotes the strength of the evidence supporting the association and not its intensity; [+]it is given when only few studies are available; [2]it tissue eosinophilia not usually detected; [#]it mainly present in rectum but possibly extending to the whole colon; with adaptations from Rossi CM, Lenti MV, Merli S, Licari A, Votto M, Marseglia GL, *et al*. Primary eosinophilic gastrointestinal disorders and allergy: Clinical and therapeutic implications. Clin Transl Allergy. 2022;12(5):e12146. doi: 10.1002/clt2.12146.

study of EoE patients from Italy, being present in almost 50% of patients with EoE, and was also detected in patients with other primary eosinophilic disorders of the gastrointestinal tract. Most patients in this series were already avoiding peaches and other LTP-containing foods, for IgE-mediated manifestations ranging from contact urticaria to anaphylaxis (64). The sensitization/allergy to Pru p 3, a cross-reactive and thermal- and acidic-resistant allergen present in the peel or seeds of many fruits and vegetables, significantly complicates the management and quality of life of patients with EoE, because it may hence impose significant further dietary restrictions in EoE patients undergoing diet therapy, especially those on 4-FED or 6-FED. On the other hand, long term PPI therapy may expose EoE patients allergic to pathogenesis-related (PR)-10 allergens to systemic reactions. Topical steroids have an important role in EoE since they induce a clinical, histological, and endoscopic improvement. They exert a direct anti-inflammatory effect on the mucosa, promote mucosal integrity, decrease fibrogenic cytokines and hence possibly fibrosis. Induction therapy, ranges from 2 to 12 weeks. Maintenance therapy at the lowest dosage should be continued possibly indefinitely, given the high risk of relapse (65). While systemic steroids EoE are generally not recommended in EoE according to therapeutical guidelines (55, 56), they have a recognized role in the treatment of non-EoE EGID especially in the case of acute severe exacerbations (66). Moreover, a surgical approach may be warranted in case of obstruction especially when muscular involvement is present. Topical steroids are usually reserved for maintenance therapy together with immunosuppressants to prevent relapses. The role of allergen-free diets is currently recommended for eosinophilic gastritis, while its role in more distal eosinophilic disorders still needs to be ascertained (62). Actively screening atopic patients for EGID could be an effective strategy to reduce the diagnostic delay of this disorders and possibly improve clinical outcomes. Male patients with atopic comorbidity and any degree of dysphagia are the patients at risk for EoE and these parameters are already considered in a diagnostic algorithm which evaluates probability of having EoE before endoscopy (67). On the other spectrum, patients at risk for eosinophilic colitis are young female with atopic disorders presenting with diarrhea and elevation of fecal calprotectin when an endoscopy is not diagnostic for inflammatory bowel disease (68).

Eosinophilic granulomatosis with polyangiitis (EGPA)

Eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome) is a rare small-vessel vasculitis that occurs in patients with asthma and eosinophilia and is histologically characterized by tissue eosinophilia, necrotizing vasculitis and eosinophil-rich granulomatous inflammation. The incidence of EGPA ranges between 0.5 and 4.2 cases per million people per year and its prevalence between 10 and 14 cases per million inhabitants globally. The frequency of the disease is comparable in men and women, and the mean age at diagnosis is ~50 years. Pediatric cases are extremely rare (69). The clinical phenotype of EGPA is quite heterogeneous and the diagnosis is not always straightforward. Anti-neutrophil cytoplasmic antibodies (ANCA), usually against myeloperoxidase (MPO), are detectable in ~40% of the cases and are associated with a different frequency of clinical manifestations: features of vasculitis, particularly glomerulonephritis, peripheral neuropathy and purpura, occur more often in ANCA-positive patients, whereas the so-called eosinophilic features such as cardiac involvement and gastroenteritis are more frequent in ANCA-negative patients (70, 71). Asthma and ear-nose-throat disease, which occur in > 90% and 60-80% of patients with EGPA, respectively, are equally distributed in the ANCA-positive and ANCA-negative groups. Histopathological evidence of vasculitis is more common in ANCA-positive than in ANCA-negative patients, although EGPA lesions usually include eosinophilic infiltrates along with necrotizing vasculitis and are therefore difficult to categorize as vasculitic or eosinophilic (72). Several cell types participate in the immunopathogenesis of the disease. Eosinophils are clearly central and are likely to mediate tissue damage, a concept supported by the evidence that targeting IL-5 (for example, using mepolizumab), a survival factor for eosinophils, is an effective therapy for EGPA (71, 72). $CD4^+$ T cells orchestrate the adaptive immune response and are polarized towards a T helper 2 (TH2) phenotype, which enhances eosinophilic reactions; however, Th1 and Th17 cells might also have a role, especially in vasculitis and granuloma formation (73). EGPA has been classically described as a three-stages disease (73). The first stage is almost always present, with asthma being documented in about 100% of EGPA cases (70, 71, 74). The other two stages can often overlap. Alternatively, some patients may never experience the vasculitic phase, while others may directly develop vasculitis without any eosinophil-related organ damage in addition to respiratory tract involvement (73). Historically, conventional treatment was with oral corticosteroids (OCS), with or without additional immunosuppressive drugs, but many patients experienced corticosteroid-related side effects or relapses during OCS tapering. As a result, healthcare resource utilization and burden of disease and treatment were high (75). Since eosinophils contribute to the pathophysiology of EGPA, and with severe eosinophilic asthma being a key feature of the disease, mepolizumab was postulated as a potential treatment option for patients with EGPA. Following the promising early findings, which showed reductions in OCS and exacerbation rates with mepolizumab, recruitment of patients with relapsing or refractory EGPA (regardless of ANCA status) who were receiving standard of care therapy began in 2014 for the Phase III MIRRA (mepolizumab in relapsing or refractory EGPA; NCT02020889) trial (76). In this 136-patient study,

Table III *- Clinical variants of HES.*

Variants of HES	Features	Epidemiology
Myeloid HES	Intrinsic defect of eosinophilic committed neoplastic progenitor cells caused by mutations	10-20% of cases
Lymphocytic HES	Clonal T lymphocytes producing cytokines such as IL-3 and IL-5 that stimulate growth, differentiation and survival of eosinophils	10-20% of cases
Overlap HES	Overlapping forms with other conditions (EGPA, EGID, IgG4-related disease)	12-32% of cases
Associated HES	Due to secondary cause such as drug reaction, infection, neoplasm, immunologic disorders	10% of cases
Familial HES	Familial forms with autosomal dominant transmission	Rare
Idiopathic HES	HES who remain unexplained after ruling out parasitic, drug-induced, inflammatory and paraneoplastic causes as well as clonal and lymphocytic	35-50% of cases

add-on mepolizumab therapy (300 mg SC) *versus* placebo, led to a reduction in blood eosinophil count and more accrued time in remission, reduced the rate of relapse, and allowed patients to decrease their OCS use. Based on these findings, mepolizumab 300 mg SC was approved for EGPA in the USA in 2017 and in Europe soon after. However, a *post-hoc* analysis using a composite endpoint comprising remission, OCS reduction, and/or being relapse free for the treatment period showed that mepolizumab provided clinical benefit in up to 87% of patients with EGPA beyond the remission-based primary endpoints (77). Early evidence of efficacy for other anti-IL-5 treatment benralizumab has also been shown (78) in recent small studies (≤ 10 patients). Benralizumab appears to be an effective treatment for refractory asthma or ear-nose-throat manifestations in EGPA and allows GC-sparing in two retrospective real-life studies (79, 80). A Phase III trial of benralizumab in EGPA is currently underway. Overall, the clinical benefits associated with eosinophil reduction in patients with EGPA confirmed that eosinophils contribute to EGPA disease pathology and supported the use of mepolizumab in eosinophil-driven diseases beyond severe eosinophilic asthma (26, 69). For his effectiveness also in EGPA, mepolizumab was recently added as a therapeutic option in EGPA guidelines (69, 81).

Hypereosinophilic syndrome (HES)

Hypereosinophilic syndromes are defined by the presence of sustained blood (> 1.5×10^9 cells/L) or tissue hypereosinophilia (HE) and presumed or proven eosinophil-mediated organ or tissue involvement (4, 82) (**table I**). HES is a rare disorder for which robust epidemiologic data are scarce. The diversity of the conditions that fall within the spectrum of HES makes it difficult to accurately capture the incidence and prevalence of HES and associated eosinophilic disorders. HES can be further subdivided into clinical variants (**table III**). Approximately 80% of myeloproliferative HES cases are caused by an interstitial deletion on chromosome 4, producing the FIPIL1-PDGFRA fusion gene which generates a constitutively active tyrosine kinase that promotes abnormal eosinophil development and altered IL-5 signaling Clinically, increased serum tryptase and vitamin B12 levels are found in myeloproliferative HES (4, 82). The clinical picture of HES is proteiform since all organs can potentially be affected. The pathogenesis of HES depends on the mechanism by which eosinophils are activated. Regardless of the subtype, HES commonly presents as a very burdensome disease, characterized by non-specific symptoms (fatigue, fever, weight loss, myalgia) and multi-organ impairment mostly involving skin, lungs, digestive tract and hear (83, 84). Main clinical manifestations of HES are resumed in **table IV**. Nowadays, given the current state of knowledge and available treatments, only clonal forms and severe cardiac involvement are truly life-threatening (85). Idiopathic HES is form of main interest for allergists and clinical immunologists. It is characterized by persistent unexplained hypereosinophilia with organ damage. After ruling out parasitic, drug-induced, inflammatory, and paraneoplastic causes as well as clonal and lymphocytic HES, around 3/4 of cases of HE/HES remain unexplained: these are referred to as idiopathic HES. This diagnosis of exclusion only requires very seldom bone marrow cytology, cytogenetic or molecular testing and the latter should be performed mainly in cases of suspected clonal HE or lymphoma (84, 85). In the last years, it is precisely mepolizumab that highlighted a possible role of T2 inflammation in idiopathic HES. Indeed, this drug, originally approved for severe T2-eosinophilic asthma, interestingly showed effectiveness also in idiopathic HES (86-88). In any cases, first line treatment for HES remains glucocorticoid therapy, in addition to treating underlying causes, if identifiable. Of the biologic therapies, mepolizumab is the best studied. A randomized, double-blind placebo-controlled phase III clinical trial showed FIP1L1-PDGFRA-negative HES patients treated with mepolizumab experienced significantly reduced flares compared to placebo leading to its approval by the FDA in 2020 and soon after by EMA (88). In a phase 2 clinical trial in patients with

Table IV *- Clinical manifestations of HES.*

Involvement	Clinical features
Cutaneous	Pruritus, eczema, urticaria, angioedema, bullae, ulceration of the limbs or mucous membranes, splinter haemorrhages, fasciitis, livedo, purpura.
Pulmonary	Asthma, bronchiolitis, bronchitis, bronchiectasis, interstitial lung disease.
Cardiac	Myocarditis, pericarditis, valvular disease, endomyocardial fibrosis, dilated cardiomyopathy, intracavitary thrombus, coronary artery vasospasm.
Neurological	Ischemic cerebrovascular disease (usually bilateral and of watershed distribution), peripheral neuropathy, myelitis
Digestive	Eosinophilic esophagitis, eosinophilic gastritis, eosinophilic enteritis and eosinophilic colitis, eosinophilic ascites, eosinophilic cholangitis.
Vascular	Arterial and/or venous thrombosis. Thromboangiitis obliterans-like vasculopathy or eosinophilic vasculitis.
Rheumatologic	Arthritis, tenosynovitis, myositis

PDGFRA-negative HES treatment with benralizumab showed reduction in the AEC during the study period, in addition to improvement in other clinical and hematologic responses compared to placebo (89). Phase III clinical trials involving benralizumab are currently underway (NCT04191304).

Discussion

The aim of this review is to highlight the state of the art regarding the knowledge of blood eosinophilia and the most important related diseases of interest, focusing particularly on those where significant advancements have been made in targeted therapy towards type 2 inflammation in recent years and to underline the important role of allergists and clinical immunologists in diagnosing and treating such pathologies. Despite peripheral eosinophilia not being the hallmark of EGID, we decided to consider them because these are emerging conditions linked to eosinophil disorders and type 2 inflammation. Primary EGID belong to the spectrum of T2 inflammation, and at the same time should be considered in the differential diagnosis of patients presenting with hypereosinophilia, especially in the setting of gastrointestinal symptoms and type 2 comorbidities. Their diagnosis of EGID is particularly challenging and may require a holistic approach integrating functional aspects from different organ systems (40, 45). More precisely, even though they are characterized by tissue eosinophilic infiltrates, peripheral eosinophilia is not generally a prominent feature and thus useful diagnostic biomarker and possibly outcome measure (50). So, a high degree of suspicion is mandatory when confronted with evocative clinical clusters, such as male sex, atopy and dysphagia for EoE (40, 43) and female sex, atopy, diarrhea/abdominal pain, elevation of fecal calprotectin for eosinophilic colitis (68). Yet, primary EGID should be distinguished from HES or EGPA with secondary gastrointestinal involvement, because the pathogenesis and hence treatment approach is different (40, 68). Indeed, at least for some of EGID, particularly EoE, eosinophil-targeted treatments as a class, as opposed to HES and EGPA, have not been successful in clinical trials, due to the fact that the clinical endpoint has not been attained, whereas dupilumab has clearly demonstrated an objective clinical and functional improvement in addition to tissue depletion of eosinophils (47, 50). For other non-EoE EGID no biological therapy is yet approved but some are under evaluation in clinical trials, so at present the main pharmacological therapies remain systemic/topical steroids and other immunosuppressants, according to the phase of disease (40). Inizio moduloRegarding the role of type 2 inflammation in asthma, CRSwNP, and EoE among EGID, it is very important and quite well defined. However, concerning EGPA and HES, despite eosinophils being the main actors, considering that these are rare diseases affecting multiple organs, the role of type 2 inflammation is still debated. EGPA has been classically described as a three-stages disease. The first stage, previously defined as "allergic", is characterized by T2-eosinophilic asthma and chronic rhinosinusitis (CRS) which can last for several years before the development of systemic manifestations. In our opinion, the term allergic is not the proper definition, since only 30-40% of EGPA patients have evidence of IgE-mediated allergic sensitization to aeroallergens (90, 91). In this sense, "T2 rhinobronchial" could be a more appropriate definition for the first stage. In the second stage, hypereosinophilia becomes systemic and involves other organs in addition to the respiratory tract (for instance eosinophilic myocarditis and gastroenteritis). However, in this context eosinophilic gastroenteritis is the expression of another T2 epithelial dysregulated response to the exposome, like asthma, rather than the evolution of a systemic T2 inflammation originating from asthma and involving internal organs. The third and last stage of EGPA is represented by polyangiitis, that is a necrotizing vasculitis of medium/small vessels, leading to clinical man-

ifestations such as glomerulonephritis, purpura, neuropathy (73). In this context, differential diagnosis between idiopathic HES and EGPA could be very challenging (92, 93), since there is a great degree of overlapping between the two conditions, even more if both diseases are considered as T2 disorders originating from T2-eosinophlic asthma. For example, in front of a patient with asthma, CRS, myocarditis and hypereosinophilia, it could be very difficult to establish if the diagnosis is EGPA (second stage) or idiopathic HES that could be defined T2-driven HES, especially in case of negative ANCA-status. However, as the name says, evidence of polyangiitis (vasculitis) should be present to make a diagnosis of EGPA. This concept was pointed out by 2022 ACR classification criteria, which introduced the entry criterion of a defined diagnosis of medium/small vessels vasculitis (81). In clinical practice, a defined diagnosis of vasculitis can be obtained through the biopsy of the suspected vasculitis-involved organ, *e.g.*, skin with purpura or kidney in presence of increased creatinine/proteinuria/hematuria. In case of neuropathy, even if this manifestation is strongly suggestive for vasculitis of vasa nervorum, it is quite difficult to establish a defined diagnosis, since nerve biopsy is not feasible in most centers. Thus, applying ACR 2022 criteria, a defined diagnosis of vasculitis could be probably obtained only in those patients presenting in an overt vasculitic stage, with typical vasculitic manifestations susceptible to bioptic procedures. In this sense, a revised nomenclature for the second non-vasculitic stage of EGPA has been suggested by some authors, who proposed the definition of "hypereosinophilic asthma with systemic non-vasculitic manifestations" (94), while other authors even proposed to consider the second stage of EGPA as idiopathic HES (95). In this way, we could propose the definition of T2-driven HES, characterized by T2-eosinophilic asthma, hypereosinophilia, negative ANCA status and systemic manifestations without vasculitic sings. Regarding EGPA, interestingly, typical vasculitic manifestations (glomerulonephritis, purpura, neuropathy) are observed much more frequently in ANCA-positive patients, which represent 30-40% of all EGPA patients (73). This strong relationship between ANCA and vasculitic manifestations could be explained by a direct role of ANCA in the pathogenesis of vasculitis. In this sense, a dual-pathogenesis model of EGPA has been recently proposed. According to this model, EGPA would be the result of the coexistence of T2-eosinophilic inflammation, responsible for asthma, CRS, and eosinophil-related organ damage (*e.g.*, myocarditis, gastroenteritis), and ANCA-mediated inflammation, responsible for vasculitic manifestations such as purpura, glomerulonephritis, neuropathy (96). ANCA would act as functional autoantibodies (type IIb hypersensitivity, Gell&Coombs) which stimulate neutrophils to attack vascular endothelial wall, configuring a proper autoimmune vasculitis, even if without immune complexes (97). The lack of activity of immune-complexes formation by ANCA would be a reasonable explanation for the pauci-immune pattern observed on direct immunofluorescence in EGPA and other ANCA-associated vasculitides, previously defined for this reason pauci-immune by the Chapel Hill consensus conference (98). These evidences may rise the question whether ANCA could be used as a biomarker of vasculitis for EGPA diagnosis, allowing to distinguish between T2-driven HES (only T2-eosinophilic inflammation) and EGPA (T2-eosinophilic inflammation plus autoimmune vasculitis). However, the verbatim application of eosinophils/ANCA dualism cannot always be translated into routine clinical practice, since clinical manifestations typical of vasculitis can be observed also in ANCA-negative patients, albeit much less frequently. An International Consensus reported poor sensitivity/specificity of ANCA in differentiating "vasculitic" from "eosinophilic" EGPA, stating that ANCA cannot guide treatment decision (99). Recent evidence suggested that therapy with monoclonal antibodies (mAbs) such as mepolizumab, benralizumab (anti-IL-5-R) and dupilumab (anti-IL4/IL-13Rα), selectively targeting T2-eosinophilic inflammation, could better elucidate the role of ANCA in the pathogenesis of vasculitis in EGPA. Indeed, some Authors recently documented relapse or new onset of ANCA-positive EGPA in patients undergoing anti-T2 mAbs for EGPA or severe asthma, respectively, accompanied by re-increase/new finding of p-ANCA positivity (100-103). In patients undergoing anti-IL-5/IL-5-R mAbs, blood eosinophilia was mild (< $1{,}000 \times 10^9$/L) or even within the normal range at the time of EGPA relapse/onset (100-103), so that it could be hypothesized that symptoms were due to raised ANCA. Anti-IL-5 mAb mepolizumab 300 mg is now approved for EGPA and idiopathic HES in USA and Europe. The efficacy of mepolizumab in both T2-eosinophilic asthma and idiopathic HES suggests a possible common IL-5-driven pathogenesis, raising the question whether IL-5 hyperexpression, as it happens in asthma, is a result of T2 inflammation also in idiopathic HES. In this sense, a continuum between the two conditions could be hypothesized, with T2-eosinophilic asthma representing the origin of a "T2-driven HES" (improperly considered idiopathic?) with involvement of other organs in addition to the lung. This hypothesis could be reasonable in those patients affected by mepolizumab-responsive idiopathic HES with documented asthma/respiratory involvement, the percentage of which ranges from 44 to 95% in clinical trials (88, 89, 104). Interestingly, Kuang *et al.* found that patients affected by idiopathic HES with pulmonary involvement were significantly more likely to respond to mepolizumab (104). The hypothesis of a T2-driven HES originating from T2-eosinophilic asthma could be even more reasonable in the context of EGPA, considered a special variant of reactive immune-mediated HES according to the latest classifications (4, 83, 84). In both HES and EGPA, disease course can vary. Some patients with HES experience recurrent flares, while others have persistent disease that requires constant treatment. On the other hand, most patients with EGPA experience exacerbations of up-

per and lower airway symptoms and/or recurrent hypereosinophilia during SCS tapering, despite successful induction of remission. HES and EGPA are both eosinophilic diseases with serious and systemic manifestations, but they present unique challenges in diagnosis and treatment. The expertise of Allergists and Clinical Immunologists is critical in identifying and managing these conditions, drawing on their understanding of the pathogenetic mechanisms underlying type 2 inflammation.

Conclusions

Type 2 (T2) inflammation represents the arm of the immune system originally deputed to the defense against parasites and helminths (105). T2 inflammation starts with the presentation of the antigen by dendritic cells (DCs) to T $CD4^+$ helper lymphocytes, which differentiate into T $CD4^+$ helper 2 (Th2) lymphocytes, with consequent production of T2 cytokines: interleukin-5 (IL-5), interleukin-4 (IL-4), interleukin-13 (IL-13). These cytokines stimulate recruitment of effector cells such as eosinophils, basophils, and mast cells, and IgE synthesis by B lymphocytes. Particularly, IL-5 is responsible for eosinophils' recruitment and activation. In predisposed subjects, a dysregulated T2 inflammation can develop in epithelial barriers (airways, intestine, skin) in response to various antigens other than parasites or helminths: allergens, microorganisms, pollutants. This dysregulated epithelial T2 response leads to diseases such as asthma, rhinitis/rhinosinusitis, eosinophilic gastrointestinal disorders (EGID), atopic dermatitis (105, 106). Allergens are not the only antigens able to trigger a dysregulated T2 inflammation, and IgE-mediated allergic sensitization can be present without clinical significance or even absent in the above-mentioned diseases. Thus, rather than allergic disorders, T2 disorders would be a more appropriate definition, including also non-allergic eosinophilic diseases such as eosinophilic asthma, chronic rhinosinusitis, EGID, EGPA and HES.
According to the heterogeneity of eosinophilic disorders a multidisciplinary approach should be adopted. In the context of a multidisciplinary team, Allergists and Clinical Immunologists with a deep knowledge of T2 inflammation and T2 disorders can better refine the eosinophilia workup and make the most appropriate diagnosis. This a very important skill since considering T2 inflammation could have important diagnostic and therapeutic implications.

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AMM, CMR, MAP: conceptualization. All authors: data curation, formal analysis, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Hereditary angioedema: 24 years of experience in a Portuguese reference center

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Key words

Hereditary angioedema; angioedema; C1-inhibitor deficiency; treatment; prophylaxis.

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Impact statement

HAE poses a high burden of disease, but there is still evidence of long diagnostic delay, especially in those without family history, emphasizing the need to raise disease awareness.

Summary

Background. *Hereditary angioedema (HAE) poses a high burden of disease, being its epidemiological and clinical data heterogeneous among countries, with no recent published studies concerning Portuguese patients. Therefore, we aimed to raise awareness of HAE and to contribute to clinical knowledge.* ***Methods.*** *An observational, descriptive, retrospective, and cross-sectional study was performed, that included a cohort of 126 patients followed in a single Portuguese center.* ***Results.*** *We observed a high prevalence of HAE-C1-INH type II (45.2% of patients). Most HAE patients (67.4%) presented the initial manifestations of the disease before adulthood, at a mean age of 12.6 ± 8.4 years. However, we found a long delay in HAE diagnosis, especially in those without family history (mean 20.7 ± 17.3 years). Stress was the most common trigger, followed by trauma and infection. Symptoms involving different systems were increasingly reported with increased disease duration. Cutaneous symptoms (95.0%) were more frequent, followed by gastrointestinal (80.7%), and respiratory symptoms (50.4%). HAE symptoms led to abdominal surgery in 22 (17.5%) patients and induced laryngeal edema requiring intubation/tracheostomy in 8 (6.3%) patients. Most patients were under long-term prophylaxis, mainly with attenuated androgens (62.7% of patients).* ***Conclusions.*** *The correct distinction between HAE and other common causes of angioedema is critical, allowing reduction of diagnostic delay, improvement of adequate management, and ultimately improving outcomes and quality of life of HAE patients.*

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant, and potentially life-threatening disease, that was first described in 1888 by Osler (1, 2).

HAE is characterized by recurrent and often unpredictable episodes of swelling, resulting from vasodilation and increased vascular permeability caused by the release of vasoactive mediators (2-4). Symptoms of HAE frequently manifest during childhood or adolescence and are lifelong persistent, but the course of the

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disease is highly variable, with different clinical presentations (1, 3, 5). HAE patients typically present episodic attacks of swelling, most frequently of the skin, gastrointestinal and upper respiratory tracts (1, 5). The most severe manifestations of HAE involve the upper airways and the gastrointestinal system, with eventual asphyxia, intense abdominal pain and unnecessary abdominal surgery as a result (6, 7). HAE is thus associated with a high burden of illness, leading to anxiety and depression, impairment of daily activities, economic costs, and decreased health-related quality of life, all influenced by the frequency and severity of the attacks (8). Although HAE attacks are often unpredictable, some triggers have been described, including stress, trauma, infection, drugs, and fatigue (3).

In most patients, HAE is caused by a mutation in the SERPING1 gene, which encodes the C1-esterase inhibitor (C1-INH), leading to the quantitative or functional deficiency of this protein (4, 9). HAE with C1-INH deficiency (HAE-C1-INH) can be classified in type I, characterized by both reduced C1-INH protein levels and function, and type II, characterized by normal or high levels of C1-INH protein that is dysfunctional. C1-INH deficiency results in an uncontrolled activation of the contact system (kallikrein-kinin system), with the consequent increased production of bradykinin that, in turn, increases vascular permeability, therefore inducing swelling (3, 9, 10). In 2000, HAE with normal C1-INH (HAE-nC1-INH) was also described (11, 12). The mechanism of swelling in this type of HAE is less understood, but evidence suggests that it is also mediated by bradykinin (3, 8). HAE-nC1-INH can be further divided into HAE caused by mutations in the factor XII gene (F12), plasminogen (PLG), angiopoetin-1 (AGPT1), kininogen 1 gene (KNG1), myoferlin (MYOF), heparan sulfate (HS)-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or with an unknown genetic cause (8, 13).

HAE has an estimated prevalence of 1:50,000 (1, 14-16). HAE-I is the most prevalent type, accounting for approximately 85% of cases, and HAE-II being responsible for approximately 15% of cases (1, 17). HAE-nC1-INH is less prevalent, but its incidence is still largely unknown (18). It is reported that approximately 25% of cases are due to *de novo* mutations (19).

Despite the crucial relevance of an early diagnosis, allowing an appropriate management of patients, HAE is still commonly misdiagnosed and considerable delays in the diagnosis of this disease still exist (15, 16, 20-22). The high variability of clinical manifestations and the frequent misdiagnosis with histamine-mediated angioedema, the absence of family history in around 25% patients, the requirement of proper interpretation of the diagnostic tests results, and the lack of diagnostic tools for the diagnosis of HA-nC1-INH, hinder timely HAE diagnosis (23).

Management of HAE patients involves three key aims: treatment of acute attacks (on-demand treatment); prevention of new attacks with long-term prophylaxis; and the prevention of attacks in periods of increased risk, such as before surgical procedures, with short-term prophylaxis (1, 8, 18, 24). HAE treatment has suffered significant improvements in the last decade (8, 18, 24, 25), but it is often suboptimal (18) and varies largely between different countries (8).

Therefore, we aimed to describe the clinical data of the largest Portuguese HAE cohort of patients. We have characterized our cohort in terms of demographics, type of disease, clinical characteristics, including age at initial manifestations and delay in diagnosis, triggers of attacks, clinical presentation, therapeutic approaches, and severity of disease.

Materials and methods

Study design, participants, and ethical considerations

This was an observational, descriptive, retrospective, and cross-sectional study, that included a sample of 126 HAE patients.

This study included all patients with confirmed diagnosis of HAE followed in Centro Hospitalar Universitário de Lisboa Norte (CHULN), Portugal, between January 1995 and July 2019. The diagnosis was based on clinical and laboratory criteria, including genetic testing when appropriate, in accordance with national (26) and international guidelines/recommendations (2, 7, 8, 18). Both symptomatic and asymptomatic HAE patients were enrolled in the study.

This study was approved by the CHULN ethics committee and was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

Demographics and clinical data collection

All data were retrieved and collected from CHULN database, between January and June 2019. For each patient, the following information was collected from medical records: gender, age, follow-up time, family clusters, patients per family, year of admission, residence area, HAE classification (HAE-C1-INH types I and II, and HAE-nC1-INH), age at initial manifestations, age at diagnosis, triggers of the disease, clinical presentation including cumulative symptoms present at the time of the initial manifestations, at the time of diagnosis and at the last clinical appointment, previous abdominal surgery, previous laryngeal attacks requiring intubation/tracheostomy and on-demand and prophylactic treatment received.

Severity of the disease was classified by attending physicians, according to the Agostoni *et al.* criteria (1), taking in consideration patients' data from the 12 months preceding the study period (**table IS**). The same period was also considered for the evaluation of treatments performed (long-term prophylaxis, short-term prophylaxis, and on-demand treatments).

All patients were included in the study, regardless of missing data.

Statistical analysis

Descriptive analysis of demographic and clinical data was performed. Categorical variables are presented as absolute (n) and relative frequencies (%), and, in general, data are presented with mean ± standard deviation (SD) (minimum and maximum) and median and 1st and 3rd quartiles (Q1-Q3), except when mentioned otherwise.

Table I *- Demographic characteristics of the cohort of HAE patients.*

Characteristics	Total (N = 126)
Gender, n (%)	
Female	70 (55.6)
Male	56 (44.4)
Age, years	
Mean ± SD (minimum-maximum)	43.6 ± 20.0 (4.0-82.0)
Median (Q1-Q3)	45.0 (28.5-57.8)
Age, n (%)	
< 18 y	16 (12.7)
≥ 18 y	110 (87.3)
Follow-up time, years	
Mean ± SD (minimum-maximum)	11.0 ± 6.4 (0.0-24.0)
Median (Q1-Q3)	10.0 (7.0-16.0)
Families, n	45
Patients per Family	
Mean ± SD (minimum-maximum)	2.8 ± 4.2 (1.0-28.0)
Median (Q1-Q3)	2.0 (1.0-3.0)
New Patients per Year	
Mean ± SD (minimum-maximum)	5.0 ± 3.6 (0.0-17.0)
Median (Q1-Q3)	4.0 (3.0-7.0)
New patients, n (%)	
≤ 2001	25 (19.8)
2002-2007	25 (19.8)
2008-2013	54 (42.9)
2014-2019 (June)	22 (17.5)
Regional distribution, n (%)	
North	1 (0.8)
Center	13 (10.3)
Lisbon and Tagus Valley	94 (74.6)
Alentejo	7 (5.6)
Algarve	9 (7.1)
Azores	2 (1.6)

HAE: hereditary angioedema; N: total number of patients; n: number of patients with available data; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation.

All descriptive statistical analyses were performed using R software (version 3.4.3). The Mann-Whitney test was applied for groups comparison, with P-value < .05 considered to indicate statistical significance.

Results

Demographic characteristics of study population

Table I shows the demographic characteristics of our cohort of 126 patients, from 45 families, of whom 55.6% were female. The mean age of HAE patients was 43.6 ± 20.0 years; 12.7% of patients were less than 18 years old. The mean follow-up time was 11.0 ± 6.4 years. The mean number of new patients included in our cohort per year was 5.0 ± 3.6. Almost half of the patients were included from 2008 until 2013 (42.9%). Most patients lived in Lisbon and Tagus Valley (74.6%) (**table I**).

Clinical classification and characteristics of HAE patients regarding age of initial manifestations and delay in diagnosis

The predominant type of HAE among the cohort of patients was HAE-C1-INH type I, which was found in 64 (50.8%) patients in 28 (62.2%) families. HAE-C1-INH type II was found in 57 (45.2%) patients in 13 (28.9%) families. HAE-nC1-INH was diagnosed in 5 (4%) patients in 4 (8.9%) families (**table IIS**).

Table II and **figure 1** show data regarding patients' age at the time of initial HAE manifestations and the diagnostic delay in the total cohort, in the index case (first HAE patient) of the family, and in subsequent patients in the same family.

The mean age at initial manifestations of the total population of HAE patients was 12.6 ± 8.4 years; 67.4% of patients presented initial manifestations before the age of 18 years. The mean age at diagnosis was 26.6 ± 16.7 years; 63.4% of patients were diagnosed aged 18 or older. This represented a mean delay in diagnosis of 14.4 ± 15.7 years (median delay of 10.0 [1.0-24.0] years); 29.4% of patients presented a delay in diagnosis of more than 20 years (**table II**).

As expected, index cases presented a significant higher diagnostic delay than subsequent familial cases (20.7 *vs* 9.9 years, respectively; p = 0.0001), with 39.2% of subsequent patients receiving a HAE diagnosis before adulthood *vs* only 13.5% of index cases. A diagnostic delay of ≥ 20 years occurred frequently in index cases (42.3%) whereas most subsequent HAE patients received a diagnosis in < 5 years (44.6%) (**table II**, **figure 1**).

Triggers and symptoms in the population of HAE patients

Disease triggers were not identified in 27.0% of patients. From the identified triggers, stress was the most frequently reported (47.6%), followed by trauma (33.3%), and infection (26.2%) (**table IIIS**).

Table II *- Age of initial HAE manifestations and delay in diagnosis in the first and subsequent HAE patients in family.*

Characteristics	Total (N = 126)	First in family* (N = 52)	Not first in family (N = 74)
Age of initial manifestations, years			
Mean ± SD (minimum-maximum)	12.6 ± 8.4 (0.0-47.0)	13.2 ± 7.2 (0.0-30.0)	12.2 ± 9.2 (0.0-47.0)
Median (Q1-Q3)	12.0 (6.0-18.0)	13.0 (8.0-18.0)	9.0 (5.5-17.0)
Age of initial manifestations, n (%)			
< 18 y	85 (67.4)	34 (65.4)	51 (68.9)
≥ 18 y	31 (24.6)	15 (28.8)	16 (21.6)
Unknown/Not reported	10 (7.9)	3 (5.8)	7 (9.5)
Age of diagnosis, years			
Mean ± SD (minimum-maximum)	26.6 ± 16.7 (0.0-70.0)	33.2 ± 16.7 (4.0-70.0)	21.8 ± 15.0 (0.0-55.0)
Median (Q1-Q3)	25.5 (13.8-37.5)	33.0 (20.0-40.0)	21.0 (9.5-30.0)
Age of diagnosis, n (%)			
< 18 y	36 (28.6)	7 (13.5)	29 (39.2)
≥ 18 y	80 (63.4)	42 (80.8)	38 (51.4)
Unknown/Not reported	10 (7.9)	3 (5.8)	7 (9.5)
Delay in diagnosis, years			
Mean ± SD (minimum-maximum)	14.4 ± 15.7 (0.0-66.0)	20.7 ± 17.3 (0.0-66.0)	9.9 ± 12.7 (0.0-43.0)
Median (Q1-Q3)	10.0 (1.0-24.0)	15.0 (8.0-30.0)	4.0 (0.0-15.8)
Delay in diagnosis (5-year groups), n (%)			
< 5	43 (34.1)	10 (19.2)	33 (44.6)
[5 - 10[	13 (10.3)	5 (9.6)	8 (10.8)
[10 - 15[	13 (10.3)	6 (11.5)	7 (9.5)
[15 - 20[	7 (5.6)	4 (7.7)	3 (4.1)
≥ 20	37 (29.4)	22 (42.3)	15 (20.3)
Unknown/not reported	13 (10.3)	5 (9.6)	8 (10.8)

HAE: hereditary angioedema; N: total number of patients; n: number of patients with available data; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation; *first patients diagnosed in a family (if 2 or more patients are diagnosed in the same initial year: they are all considered as "First in family").

Figure 1 *- Age (years) at diagnosis* ***(a)*** *and delay (years) in diagnosis* ***(b)*** *in first and subsequent hereditary angioedema patients in family. Presented data corresponds to the percentage of patients with available data.*

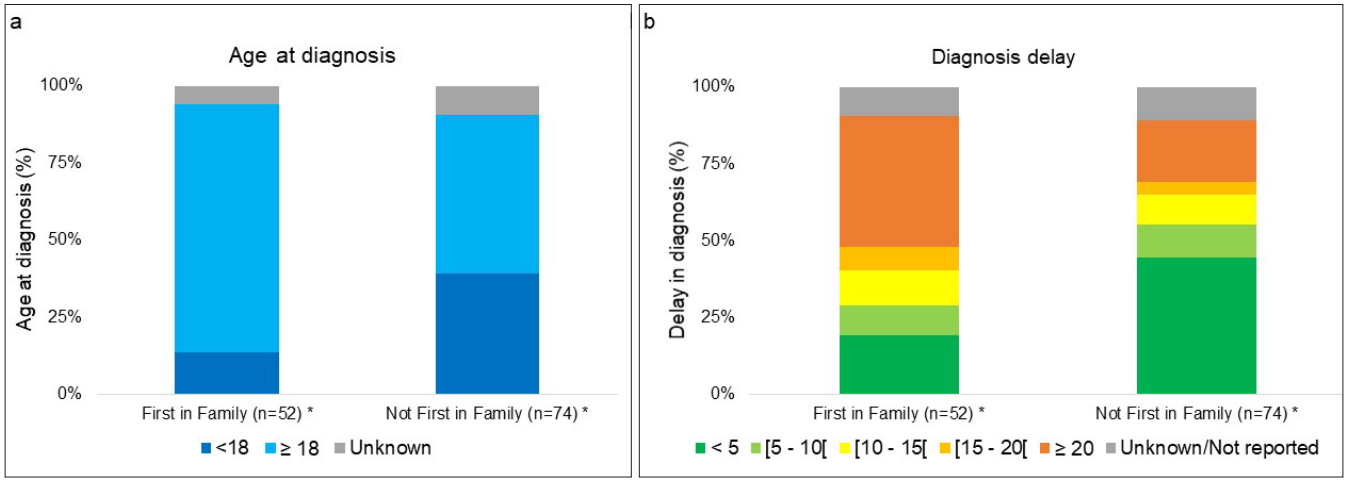


Table III - *Cumulative symptoms present at disease onset, at the time of diagnosis and at the last clinical appointment (current).*

Characteristics	At disease onset	At the time of diagnosis	Current
Asymptomatic patients, n (%)	14 (11.1)	14 (11.1)	7 (5.6)
Symptomatic patients, n (%)	112 (88.9)	112 (88.9)	119 (94.4)
Number of systems involved per patient			
Median (Q1-Q3)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (2.0-3.0)
Systems involved, n (%)			
Cutaneous only	48 (42.9)	29 (25.9)	14 (11.8)
Gastrointestinal only	21 (18.8)	7 (6.3)	6 (5.0)
Respiratory only	2 (1.8)	3 (2.7)	0 (0.0)
Cutaneous+Gastrointestinal only	27 (24.1)	41 (36.6)	39 (32.8)
Cutaneous+Respiratory only	3 (2.7)	9 (8.0)	9 (7.6)
Gastrointestinal+Respiratory only	1 (0.9)	2 (1.8)	0 (0.0)
Cutaneous+Gastrointestinal+Respiratory	10 (8.9)	19 (17.0)	51 (42.9)
Frequency of Cut, GI or Resp symptoms, n (%)			
Cutaneous	88 (78.6)	98 (87.5)	113 (95.0)
Gastrointestinal	59 (52.7)	69 (61.6)	96 (80.7)
Respiratory	16 (14.3)	33 (29.5)	60 (50.4)

HAE: hereditary angioedema; Cut: Cutaneous; GI: Gastrointestinal; Resp: Respiratory; n: number of patients with available data; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation.

Table III shows the cumulative reported symptoms at disease onset, at the time of diagnosis, and current (last clinical record) symptoms. Cutaneous symptoms were the most frequently reported clinical presentation, as initial (78.6%), at the time of diagnosis (87.5%) and as current manifestations (95%). Gastrointestinal and respiratory symptoms were reported as initial symptoms by 52.7% and 14.3% of patients, respectively, at the time of diagnosis by 61.6% and 29.5%, and as current manifestations by 80.7% and 50.4% of HAE patients (**table III**).

HAE symptoms led to abdominal surgery in 22 (17.5%) patients and induced laryngeal edema requiring intubation/tracheostomy in 8 (6.3%) patients.

Therapeutic approaches for the management of HAE

Figure 2 summarizes the long-term and short-term prophylaxis, and on-demand treatment, during the previous year, for the management of HAE in the total cohort of HAE patients.

Long-term prophylaxis was used by 71.4% of HAE patients: in 37.5% of HAE children and adolescents and in 76.4% of adult HAE patients. Short-term prophylaxis with plasma-derived C1-INH concentrate was administered in 20.6% of HAE patients: in 12.5% of HAE children and adolescents and in 21.8% of adult HAE patients. Seventy-six percent of HAE patients were treated with on-demand treatment, and similar frequencies were observed between pediatric and adult patients.

Table IV describes HAE patients' data regarding drugs for long-term and short-term prophylaxis, and for on-demand treatment by age group.

Attenuated androgens were used by 70.9% of adult HAE patients as long-term prophylaxis. HAE children and adolescents received long-term prophylaxis with antifibrinolytics in 31.2% of patients. Thirty-nine percent of patients aged 18 or older were medicated with on-demand attenuated androgens (increase of regular androgen dosage or pure on-demand treatment). One adolescent was also under androgens as on-demand treatment. On-demand treatment with antifibrinolytics was used by 31.7% of the patients, mainly in pediatric patients (43.8%).

On-demand plasma-derived C1-INH concentrate was administered in 25.4% of patients, predominantly in patients younger than 18 years (37.5%). Sixteen percent of adult patients received on-demand icatibant. No children or adolescents were treated with icatibant throughout one year of therapeutic (**table IV**).

Severity of the disease

The mean degree of severity of disease was 2.6 ± 1.3 (Agostoni *et al.* (1)). Eighty-three patients presented a moderate-severe form of HAE, in contrast with 24 patients classified as asymptomatic. In all patients (index or subsequent cases), clinicians most frequently reported a score of 2 (moderate), followed by a score 5 (asymptomatic) (50% and 19%, respectively) of HAE severity (**table IVS**).

Figure 2 *- Long-term prophylaxis, short-term prophylaxis, and on demand treatment used for the management of HAE in the total cohort. The values represent the number (percentage) of patients.*

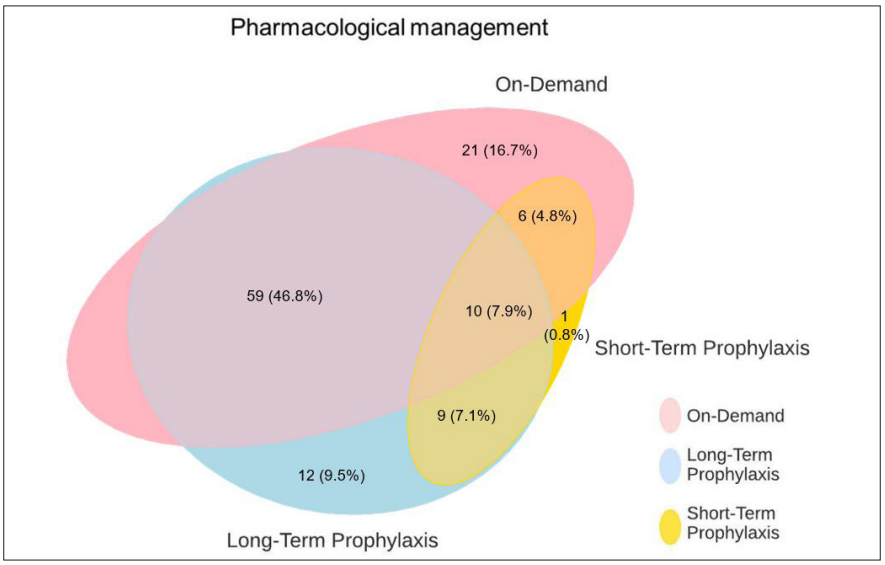


Table IV *- Long-term prophylaxis, short-term prophylaxis and on-demand treatment for the management of HAE, by age group.*

Characteristics	Total (N = 126)	< 18 y (N = 16)	≥ 18 y (N = 110)
Long-term, n (%)			
Attenuated androgens	79 (62.7)	1 (6.3)	78 (70.9)
Antifibrinolytic	10 (7.9)	5 (31.2)	5 (4.5)
Plasma-derived C1-INH	1 (0.8)	0 (0.0)	1 (0.9)
Without LTP	36 (28.6)	10 (62.5)	26 (23.6)
Short-term, n (%)			
Plasma-derived C1-INH	26 (20.6)	2 (12.5)	24 (21.8)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.0]	1.5 [1.2 - 1.8]	1.0 [1.0 - 2.0]
On-demand, n (%)			
Attenuated androgens[1]	44 (34.9)	1 (6.2)	43 (39.1)
Median of administrations [Q1-Q3]	3.0 [2.0 - 6.2]	NA	3.0 [2.0 - 5.5]
Antifibrinolytic	40 (31.7)	7 (43.8)	33 (30.0)
Median of administrations [Q1-Q3]	3.0 [2.0 - 3.2]	3.0 [2.0 - 3.5]	3.0 [2.0 - 3.0]
Plasma-derived C1-INH	32 (25.4)	6 (37.5)	26 (23.6)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.2]	1.5 [1.0 - 2.8]	1.0 [1.0 - 2.0]
Icatibant	18 (14.3)	0 (0.0)	18 (16.4)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.0]	NA	1.0 [1.0 - 2.0]
Fresh frozen plasma	0 (0.0)	0 (0.0)	0 (0.0)
Median of administrations [Q1-Q3]	NA	NA	NA

HAE: hereditary angioedema; N: total number of patients; n: number of patients with available data; NA: not applicable; Q1: 1st quartile; Q3: 3rd quartile; [1]attenuated androgens are not recommended as on-demand treatment: but the start of attenuated androgens and/or its increase of dosage were included as on-demand treatment.

Discussion and conclusions

With this study we aimed to contribute with valuable data to increase the clinical knowledge concerning Portuguese HAE patients. Since our country has approximately 10 million inhabitants, we expect an estimated 200 patients, according to the widely reported prevalence of 1:50,000 (8), meaning that our cohort represents more than half of all HAE patients living in Portugal.

We found that, although most patients presented HAE-C1-INH type I (51%), there was an overrepresentation of HAE-C1-INH type II (45%) in our cohort, which could be partially explained by the inclusion of a numerous family consisting of 28 members diagnosed with the latter type of the disease. However, even when analyzing the families included, 29% of families have HAE-C1-INH type II, which is much more than the 15% usually reported in the literature (1, 15, 16, 21, 27-32). HAE-nC1-INH was less prevalent among our cohort of HAE patients, in line with the literature (18, 30).

We observed that most HAE patients (67.4%) presented the initial manifestations of the disease before adulthood, ranging from the first year of life, until the age of forty-seven. These results are comparable with other studies (15, 21, 22, 28, 31), but slightly different results were also reported. Interestingly, a higher mean age at the initial manifestations was found in a Chinese (33) and in a Korean (29) cohort of HAE patients, and a lower median age was observed in a Brazilian cohort (34). These heterogeneous findings are certainly multifactorial, but may be partially explained by the different exposure to triggers across the world, as well as by genetic differences between these populations. Nevertheless, our findings support that HAE manifestations usually start during childhood and adolescence (20).

Despite presenting the initial HAE manifestations before 18 years, most patients (63.4%) are only diagnosed during adulthood. This significant delay in diagnosis was similar to the reported in a Swiss cohort (21) but lower compared to other studies (20, 22, 28, 31, 33). An even lower mean delay in diagnosis was reported in a Korean cohort of HAE patients, likely related to the later age of initial symptoms (29).

Our results also show that index cases present a longer delay in diagnosis compared to patients with an already identified family history of the disease. This is in accordance with the results reported by Schoffl *et al*. and Magerl *et al*. (15, 22). Moreover, a substantial reduction in the delay of diagnosis in patients born after 1980, compared with those born before 1960, was also previously reported (15), and observed in our study (data not shown). The presence of HAE family history and the increased HAE awareness by clinicians over the last decades, have likely been key in the earlier diagnosis in younger generations (5).

Stress was the most frequently reported trigger, followed by trauma, and infection. Those results are in accordance with other studies (28, 29). In a Swedish cohort, trauma and stress were also the main triggers (16). In the Swiss cohort, stress and trauma were again the most common triggers of HAE, but hormones were notably the third most common trigger (21), as has also been described by Fragnan *et al.* (31). This difference may be explained by the fact that we did not apply a category of "Hormones" or "Hormonal variations", but separate categories of "Contraception" and "Menstruation". Infection triggered the disease in 27.3% of patients from the Swiss cohort (26), a similar value to the one found in our study.

It should be noted that in our cohort almost one third of HAE patients did not identify an obvious trigger of the disease, a similar frequency when compared with the Swiss cohort (21), but lower when compared to other studies (16, 29).

As expected, with longer disease duration, symptoms from different organs/systems are increasingly reported. Cutaneous symptoms were the most frequent, followed by gastrointestinal and respiratory symptoms. These results are comparable to what has previously been reported (16, 22, 28, 31). It is well known that HAE patients often undergo unnecessary abdominal surgeries, as those attacks mimic the symptoms of acute abdominal emergencies (1-3, 5, 6). In our study, the prevalence of patients submitted to abdominal surgery was similar to the reported in the Greek cohort (20). Asphyxia occurred in 6.3% of patients, a lower value when compared to the Greek cohort in which 14% of patients were reported to undergo tracheal intubation or cricothyrotomy (20). In a study with a German cohort of 123 patients with HAE-C1-INH, the authors reported that approximately half of the individuals experienced laryngeal edema episodes (35). From those, 6 patients required intubation or cricothyrotomy (35). Although there were no registered deaths in our study, the mortality rate due to asphyxiation by laryngeal angioedema has been reported to range from 25% to 40%, in HAE patients who are not properly treated (1, 7, 35). An effective emergency treatment plan and the availability of effective self-administered on-demand treatment, like the bradykinin B2 receptor antagonist, icatibant, in most of our patients are probably key in the absence of lethality in this study. Nevertheless, the possibility of this outcome emphasizes not only the urgency of the correct and early diagnosis and management of HAE, but also the need for emergency airway management procedures, during progressive upper airway attacks in these patients. It also highlights the need for a health care provider, with HAE-specific knowledge, in close contact with the emergency department.

In order to achieve complete control of the disease, attenuated androgens, such as danazol, and antifibrinolytics, such as tranexamic acid, have been conventionally used as the main treatment options for long-term prophylaxis (3). In this study, two thirds of our patients presented a moderate to severe degree of disease severity, according to the Agostoni *et al.* classification (1), possibly explaining the high number of patients under long-term prophylaxis (71.4%), mainly accomplished using attenuated androgens. In a

Swiss cohort, only one third of patients were on a prophylactic treatment, mostly under danazol (21). Nevertheless, the percentage of patients undergoing long-term prophylaxis in our cohort was lower than the 87% reported in a Brazilian cohort (31). This result may be explained by the fact that these authors addressed the prophylactic treatment in symptomatic HAE patients (31), whereas our cohort included both symptomatic and asymptomatic patients. However, it is clear that scientific and clinical progress, combined with the development of novel, safer and more effective therapeutic approaches, have contributed to significant changes in the management of HAE patients in recent years (8, 24). It should be noted that several new management approaches are currently approved or under investigation, and that androgens are currently only recommended as second-line long-term prophylaxis (24, 25). Since the end of this study, four patients in our cohort, representing 20% of patients classified as severe disease, switched from androgen treatment to lanadelumab. This treatment became available in Portugal only since June 2020, after approval of the regulatory authorities and under special conditions.

The key strengths of our study included the analysis of a large group of HAE patients in Portugal, the inclusion of patients from different Portuguese regions, and the prolonged follow-up time. On the other hand, our study presents some limitations which must be acknowledged, namely the retrospective nature of the study and the absence of patient-reported outcomes measures data. These latter tools are applied to assess control and quality of life in patients with recurrent angioedema (Angioedema Activity Score (AAS), Angioedema Control Test (AECT), Angioedema Quality of Life (AE-QoL)), and include the more recently HAE-specific validated questionnaires, such as Hereditary Angioedema Activity Score (HAE-AS) and Hereditary Angioedema Quality of Life (HAE-QoL) (36, 37), which were not available and routinely applied at the time of the study. It is also not possible to generalize our data to other centers in Portugal, given that HAE-specific treatments are not available in many hospitals across the country.

In conclusion, this was the first study addressing HAE clinical data in a large group of patients from different Portuguese regions, thus contributing to a better understanding of this disease.

Overall, our data is in line with the literature regarding age of initial manifestations, age at diagnosis, delay in diagnosis, triggers and clinical presentation of the disease. However, we identified a higher-than-expected prevalence of HAE type II patients and families. More studies are required to confirm this result at a national level, and to understand the possible reasons underlying this difference.

As in other countries, our data supports that a long delay in diagnosis of HAE still exists, especially for those without family history of the disease.

Our data also shows a high use of attenuated androgens in long-term prophylaxis and even the use of these drugs as on-demand treatment. This situation emphasizes the need to implement an easy access to safer and more effective treatments, which is currently limited, frequently due to financial constraints.

Increased HAE awareness is still urgently needed in Portugal. The correct distinction between common causes of angioedema and HAE is critical to ensure minimal diagnostic delays and adequate treatment, ultimately leading to better outcomes and quality of life of HAE patients.

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Contributions

CV, MBF, ASS: conceptualization, formal analysis, visualization, writing – original draft, writing – review & editing. CV, LEC, SLdS, CC, RL, MIS, AL, JCa, JCo, EA, JM, FCD, NPF, MN, EP, MBF, ASS: data curation.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Variables predicting clinical remission among adults with severe asthma treated with biologic agents

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Key words

Severe asthma; remission; biologics; forced expiratory volume in 1 second.

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Impact statement

Biologic agents provide significant clinical remission rates in severe asthma. FEV1% predicted is important in predicting clinical response, with higher FEV1% predicted being associated with a higher probability of remission.

Summary

Background. *Although biologic agents promise a short- to medium-term remission in asthma, it is unclear whether they can fundamentally alter disease course and achieve long-term remission. We aimed to investigate the clinical remission success of biologics in patients with severe asthma and the factors associated with remission.* ***Methods.*** *Adults followed-up due to severe asthma who were treated with mepolizumab or omalizumab were included in the study. Sociodemographic and clinical characteristics were reviewed. Subjects with and without clinical remission at 12 and 36 months were identified. Comparisons between the groups were made with univariate and multivariable analyses.* ***Results.*** *Seventy-four patients were included in the study. The mean age of subjects was 51.85 (standard deviation = 11.43) years, and 50 (67.57%) were females. The 12- and 36-month remission rates were 72.97% and 51.79%, respectively. Patients with and without remission were similar in terms of age and gender distribution. FEV1% predicted ($p = 0.009$) and FEV1/FVC ratio ($p = 0.039$) were significantly higher in those with remission at 12 months compared to those without. FEV1 ($p < 0.001$), FEV1% predicted ($p < 0.001$) and FEV1/FVC ratio ($p = 0.004$) were significantly higher in those with remission at 36 months compared to those without. Multivariable logistic regression revealed that higher FEV1% predicted was the only factor independently associated with remission for both time points.* ***Conclusions.*** *Omalizumab and mepolizumab provide significant clinical remission rates in severe asthma. FEV1% predicted is a variable that can independently predict clinical remission among severe asthmatics receiving biologic agents.*

Introduction

Asthma is the most common chronic respiratory disease affecting more than 300 million people worldwide with significant morbidity and mortality (1). It is a heterogeneous disorder characterized by variable symptoms affecting breathing and airflow, and it is usually associated with airway hypersensitivity and chronic inflammation (1, 2).

Persistent or recurrent inflammation of the airways can cause changes in mucus-secreting cells, subepithelial fibrosis, muscle cell hyperplasia, angiogenesis, and airway structural changes such as epithelial hyperplasia and metaplasia (3, 4). Although these changes sometimes pose the risk of irreversible airway remodeling and/or fixed airflow limitation, it is known that remission may be achieved in some patients (5, 6). Although inhaled corticosteroids and bronchodilators are employed as the

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primary therapies, they have questionable efficacy in limiting progression (7). Biologic therapies spearheaded by anti-immunoglobulin (Ig) E, anti-eosinophilic (mepolizumab, benralizumab, reslizumab) and anti-interleukin (IL)-4/-13 (dupilumab) therapies have been investigated in order to block the pathophysiology of asthma (8, 9). These agents have demonstrated remarkable success in reducing asthma exacerbations and systemic corticosteroid use, particularly in moderate to severe asthma (8). Although biologic agents can target the airway inflammation and promise to achieve short- to mid-term remission in asthma, there is no conclusive information on whether they can fundamentally alter the course of asthma and provide long-term remission (1).

Clinical remission is considered in the absence of significant asthma symptoms, optimization/stabilization of lung functions, patient/provider agreement on remission, and no use of systemic corticosteroids for at least 12 months. Complete remission is considered if clinical remission is accompanied by resolution of asthma-related inflammation and if appropriate, negative bronchial hyperresponsiveness (5). In many studies, these definitions have been accepted as criteria for asthma remission with or without medication (10-12). Few studies have investigated remission of more than 12 months with the use of biologic agents in severe asthma (13-15). The proposed predictors of asthma remission are asthma severity (16, 17), lung functions (16), asthma control (18), age at onset of asthma (19, 20), duration of the disease (20), inflammation (21), comorbidities (20), and smoking status (16). Disease severity and treatment administration are the two most important factors that can affect remission in asthma. While the chance of remission of the disease is less in moderate to severe asthma, the probability of remission is higher in cases of mild asthma (22). In addition, remission rates are higher in patients who receive treatment compared to those who do not (23).

It may not be possible to achieve complete remission in all cases of asthma (8), despite the fact that biologic agents have increased the likelihood of clinical remission in severe asthma. Data is insufficient on demonstrating remission longer than 12 months and there is a lack of knowledge concerning factors that affect remission success. Retrospective real-life data is needed regarding this issue. Therefore, we aimed to investigate the clinical remission success of two biologic agents, omalizumab (anti-IgE) and mepolizumab (anti-IL-5), in patients with severe type 2 asthma and to investigate factors affecting remission.

Materials and methods

Study design, setting and population

This retrospective study was carried out at the allergy clinic in a tertiary chest diseases hospital. The study population consists of adults followed up with the diagnosis of severe asthma and treated with biologics in the clinic between January 2010 and December 2022. Exclusion criteria were using the biologic agent for less than a year, failure to attend follow-up visits regularly, switch in the biological agent administered and having missing data for the main variables included in the study.

Ethical considerations

Ethical approval was acquired from the local ethics committee (December 28th 2022/KAEK-15/2615). The study was carried out according to the ethical standards stated in the Declaration of Helsinki and its amendments, and all patients were examined and included with respect to good clinical practice guidelines.

Data collection

Study data were obtained by retrospective scanning of the hospital computerized registry and patient files. The following parameters pertaining to the time of initiation of the biologic agents were examined and recorded for the study: age and gender, body mass index (BMI), smoking status, concomitant conditions including nasal polyps, rhinitis, atopy history, respiratory disease triggered by non-steroidal anti-inflammatory drugs (NSAIDs) and other chronic and psychiatric diseases. The asthma-related parameters collected in detail were as follows: age at asthma onset, family history of asthma, biologic agent used (omalizumab or mepolizumab) and duration of treatment, oral corticosteroid (methylprednisolone) use and dosage, asthma control test (ACT) results, blood total IgE levels, eosinophil counts, and pulmonary function test results.

Definitions

Definitions related to asthma and its treatment

The diagnosis of severe asthma was made and the eligibility and administration protocol for omalizumab and mepolizumab treatments were assessed in accordance with the current guidelines (2). Briefly, patients with type 2 asthma and non-allergic eosinophilic phenotype were started on mepolizumab, whereas those with allergic phenotype were started on omalizumab. Omalizumab treatment dose and frequency of administration were calculated from a standard scale according to weight and total IgE value. According to this scale, patients received subcutaneous omalizumab at a calculated dose every 2 or 4 weeks. Mepolizumab was administered at a standard dose every 4 weeks. Clinical and biological data including ACT score, exacerbations, need of maintenance systemic corticosteroid treatment, pulmonary function tests and laboratory analyses were recorded at each visit scheduled at 4-week intervals. Asthma exacerbations were documented by scanning the hospital records after the initiation of the biological agent. The requirement to use systemic corticosteroid for at least 3 days to control aggravated asthma symptoms was defined as an exacerbation (24).

Table I *- Summary of patient and treatment characteristics with regard to 12-month remission.*

		12-months remission		
	Total (n = 74)	**No (n = 20)**	**Yes (n = 54)**	**P-value**
Age, years	51.85 ± 11.43	52.45 ± 10.33	51.63 ± 11.90	0.786
Gender				0.571
Male	24 (32.43%)	8 (40.00%)	16 (29.63%)	
Female	50 (67.57%)	12 (60.00%)	38 (70.37%)	
Body mass index, kg/m^2	30.01 ± 5.51	28.69 ± 5.22	30.50 ± 5.58	0.211
Smoking status				0.193
Active smoker	7 (9.59%)	3 (15.00%)	4 (7.55%)	
Ex-smoker	21 (28.77%)	8 (40.00%)	13 (24.53%)	
Non-smoker	45 (61.64%)	9 (45.00%)	36 (67.92%)	
Atopy	54 (72.97%)	17 (85.00%)	37 (68.52%)	0.261
Respiratory disease triggered by NSAIDs	20 (27.03%)	6 (30.00%)	14 (25.93%)	0.956
Asthma history in family	25 (34.72%)	9 (47.37%)	16 (30.19%)	0.285
Nasal polyp	36 (48.65%)	8 (40.00%)	28 (51.85%)	0.520
Rhinitis/Rhinosinusitis	29 (39.19%)	8 (40.00%)	21 (38.89%)	1.000
Obstructive sleep apnea syndrome	13 (17.57%)	6 (30.00%)	7 (12.96%)	0.165
Gastroesophageal reflux disease	2 (2.70%)	1 (5.00%)	1 (1.85%)	0.470
Psychiatric disease	3 (4.05%)	1 (5.00%)	2 (3.70%)	1.000
Cardiovascular disease/Hypertension	21 (28.38%)	8 (40.00%)	13 (24.07%)	0.289
Diabetes mellitus	12 (16.22%)	3 (15.00%)	9 (16.67%)	1.000
Age at asthma onset	31.59 ± 12.50	29.95 ± 13.56	32.21 ± 12.16	0.495
Biological treatment				0.124
Omalizumab	51 (68.92%)	17 (85.00%)	34 (62.96%)	
Mepolizumab	23 (31.08%)	3 (15.00%)	20 (37.04%)	
Systemic corticosteroid use	46 (62.16%)	10 (50.00%)	36 (66.67%)	0.297
Asthma control test	15.74 ± 4.40	14.55 ± 4.37	16.19 ± 4.37	0.157
Total IgE, IU/mL	195 (81-409)	242.5 (73-330)	182.5 (81-471)	0.942
Eosinophil, cell/μL	273.5 (100-573.5)	165.5 (61.5-640)	334 (100-573.5)	0.255
FEV1	2026.70 ± 800.45	1756.50 ± 732.63	2126.78 ± 807.68	0.077
FEV1% predicted	69.64 ± 18.56	60.50 ± 15.16	73.02 ± 18.68	**0.009**
FEV1/FVC % predicted	74.89 ± 9.41	71.20 ± 10.89	76.26 ± 8.51	**0.039**
Biological agent treatment duration (months)	54.5 (35-67)	57.5 (43-67.5)	52 (28-67)	0.223

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables and as frequency (percentage) for categorical variables; NSAID: non-steroidal anti-inflammatory drugs; FEV1: forced expiratory volume; FVC: forced vital capacity.

Definition of remission

Clinical remission comprised 12 or more months with 1) absence of significant symptoms by validated instrument; 2) lung function optimization/stabilization; 3) patient/provider agreement regarding remission; and 4) no use of systemic corticosteroids (5). ACT was used in the present study to confirm the absence of asthma symptoms. An ACT score of ≥ 20 was considered well-controlled asthma (25). An improvement of more than 10% from baseline FEV1 % predicted was considered to demonstrate lung function optimization/stabilization (4).

Table II *- Significant factors independently associated with the 12-months remission, logistic regression analysis.*

	β coefficient	Standard error	P-value	Exp(β)	95%CI for Exp(β)	
FEV1 % predicted	0.041	0.017	**0.013**	1.042	1.009	1.076
Constant	-1.753	1.105	0.113	0.173		

Nagelkerke R^2 = 0.133; CI: confidence interval; FEV1: forced expiratory volume.

In the present study subjects who met all four remission criteria for at least 12 consecutive months while receiving biologic agents were defined as having remission for 12 months, and those who did so for at least 36 consecutive months were defined as having 36 months of remission.

Outcomes

The main outcomes of this study were to determine the 12-month and 36-month clinical remission rates in severe asthma patients receiving omalizumab or mepolizumab treatment, and to determine independent factors affecting remission success among recipients of these agents.

Statistical analysis

Statistical significance was set at $p < 0.05$ for all analyses. SPSS v25.0 (IBM, NY, USA) was used for data analysis. The normal distribution of continuous variables was assessed using Shapiro-Wilk tests. Normally distributed variables were analyzed with the Student's t-test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Contingency tables were primarily analyzed with appropriate Chi-square tests, while the Fisher's exact test or its extension, the Fisher-Freeman-Halton test, were used when called for by the data. Multivariable logistic regression (forward conditional) was employed to identify independent factors associated with remission. The models created for each time point (12 months and 36 months) included significant variables from the respective univariate analyses.

Results

A total of 74 patients were included in the study. The mean age of the subjects was 51.85 (standard deviation = 11.43) years, and 50 (67.57%) were females. When the patients were evaluated according to the status of being in remission for 12 months, there were 54 (72.97%) patients who were in remission and 20 (27.03%) patients who were not. There was no significant difference between the two groups in terms of age and gender distribution ($p = 0.571$). The mean forced expiratory volume (FEV1) % predicted ($p = 0.009$) and FEV1/forced vital capacity (FVC) ratio ($p = 0.039$) were significantly higher in those with 12-month remission. While 12-month remission rate was 66.66% in omalizumab users, this rate was 86.95% in mepolizumab users. However, there was no significant difference in 12-month remission between the users of the two drugs ($p = 0.124$). The groups were also similar with regard to other variables (**table I**).

Multivariable logistic regression was performed to determine significant factors independently associated with 12-months remission. Higher FEV1% predicted (OR 1.042, 95%CI 1.009-1.076, $p = 0.013$) was independently associated with greater likelihood of 12-month remission, whereas FEV1/FVC ratio ($p = 0.665$) was non-significant (**table II**).

When the 36-month remission assessment was made, 29 (51.79%) patients were in remission, while 27 (48.21%) patients were not in remission. The groups were similar in terms

Table III *- Summary of patient and treatment characteristics with regard to 36-month remission.*

		36-months remission		
	Total (n = 56)	**No (n = 27)**	**Yes (n = 29)***	**P-value**
Age, years	51.61 ± 11.45	53.07 ± 10.48	50.24 ± 12.32	0.360
Gender				0.848
Male	19 (33.93%)	10 (37.04%)	9 (31.03%)	
Female	37 (66.07%)	17 (62.96%)	20 (68.97%)	
Body mass index, kg/m^2	29.39 ± 5.17	29.58 ± 5.53	29.20 ± 4.90	0.787
Smoking status				0.669
Active smoker	7 (12.73%)	3 (11.11%)	4 (14.29%)	
Ex-smoker	13 (23.64%)	8 (29.63%)	5 (17.86%)	
Non-smoker	35 (63.64%)	16 (59.26%)	19 (67.86%)	

→

		36-months remission		
	Total (n = 56)	**No (n = 27)**	**Yes (n = 29)***	**P-value**
Atopy	43 (76.79%)	21 (77.78%)	22 (75.86%)	1.000
Respiratory disease triggered by NSAIDs	16 (28.57%)	7 (25.93%)	9 (31.03%)	0.899
Asthma history in family	20 (37.04%)	12 (46.15%)	8 (28.57%)	0.291
Nasal polyp	26 (46.43%)	10 (37.04%)	16 (55.17%)	0.275
Rhinitis/Rhinosinusitis	21 (37.50%)	10 (37.04%)	11 (37.93%)	1.000
Obstructive sleep apnea syndrome	12 (21.43%)	8 (29.63%)	4 (13.79%)	0.264
Gastroesophageal reflux disease	2 (3.57%)	1 (3.70%)	1 (3.45%)	1.000
Psychiatric disease	3 (5.36%)	1 (3.70%)	2 (6.90%)	1.000
Cardiovascular disease/Hypertension	17 (30.36%)	11 (40.74%)	6 (20.69%)	0.180
Diabetes mellitus	6 (10.71%)	3 (11.11%)	3 (10.34%)	1.000
Age at asthma onset	31.25 ± 12.55	30.74 ± 13.41	31.75 ± 11.89	0.769
Biological treatment				0.852
Omalizumab	44 (78.57%)	22 (81.48%)	22 (75.86%)	
Mepolizumab	12 (21.43%)	5 (18.52%)	7 (24.14%)	
Systemic corticosteroid use	30 (53.57%)	13 (48.15%)	17 (58.62%)	0.605
Asthma control test	15.14 ± 4.38	14.33 ± 4.41	15.90 ± 4.28	0.184
Total IgE, IU/mL	207 (85-441.5)	171 (84-328)	217 (86-567)	0.305
Eosinophil, cell/μL	205 (98-560)	200 (63-558)	222 (100-600)	0.516
FEV1	2,116.96 ± 806.31	1,698.15 ± 716.75	2,506.90 ± 688.05	**< 0.001**
FEV1% predicted	70.89 ± 19.69	59.70 ± 16.33	81.31 ± 16.76	**< 0.001**
FEV1/FVC% predicted	74.13 ± 9.75	70.33 ± 9.53	77.66 ± 8.71	**0.004**
Biological agent treatment time, months	63 (48.5-69)	63 (43-69)	64 (50-69)	0.675

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables and as frequency (percentage) for categorical variables; *eighteen patients were not included in the analysis due to follow-up time was lower than 36 months; NSAID: non-steroidal anti-inflammatory drugs, FEV1: forced expiratory volume, FVC: forced vital capacity.

of age (p = 0.360) and gender distribution (p = 0.848). FEV1 (p < 0.001), FEV1% predicted (p<0.001), and FEV1/FVC ratio (p = 0.004) were significantly higher in those with 36-month remission. As in the 12-month remission assessment, 36-month remission rates were not statistically different between omalizumab (50.00%) and mepolizumab (58.33%) users (p = 0.852). None of the remaining variables demonstrated any significant difference between the two groups (**table III**).

Multivariable logistic regression was performed to determine significant factors independently associated with 36-months remission. Higher FEV1% predicted (OR 1.089, 95%CI 1.037-1.142, p = 0.001) was independently associated with greater likelihood of 36-month remission. Other variables in the model, FEV1 (p = 0.208), and FEV1/FVC ratio (p = 0.929) were found to be non-significant (**table IV**).

Discussion and conclusions

In the present study 12-month and 36-month remission rates are 72.97% and 51.79%, respectively, among patients with severe asthma using biologic agents. Having a higher baseline level of FEV1% predicted is the only independent predictor associated with both 12-month and 36-month clinical remission.

Table IV *- Significant factors independently associated with the 36-months remission, logistic regression analysis.*

	β coefficient	**Standard error**	**P-value**	**Exp(β)**	**95%CI for Exp(β)**	
FEV1 % predicted	0.085	0.025	**0.001**	1.089	1.037	1.142
Constant	-5.905	1.750	0.001	0.003		

Nagelkerke R2 = 0.412; CI: confidence interval, FEV1: forced expiratory volume.

Current biological agents such as omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab are effective on IL-4, IL-5, IL-13 and IgE, which are involved in the type 2 inflammatory cascade. Effective monoclonal antibody therapies are now increasingly used in asthma (26, 27). This offers promise for targeting asthma remission as a potential therapeutic goal. Omalizumab was approved in 2003 for severe allergic asthma and has been used safely and effectively to prevent asthma exacerbations (28). Mepolizumab was the first biologic targeting IL-5 and was approved in 2015 for the clinical treatment of severe eosinophilic asthma (8). In the current study, omalizumab was found to result in a 12-month remission rate of 66.66% and a 36-month remission rate of 50%. For mepolizumab, 12-month remission rate was 86.95% and 36-month remission rate was 58.33%. In the study Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO), 83.8% of subjects had uncontrolled asthma at baseline. About 50% of subjects achieved asthma control while using omalizumab (10). Exacerbation rates were also significantly reduced with omalizumab (from 3.00 ± 3.34 events at baseline to 0.78 ± 1.37 events at 12 months). Omalizumab therapy also resulted in a >50% event reduction in 77.8% of patients, while 64.7% of patients experienced a ≥3 points reduction in ACT score (10). In the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study, the results of 32-week mepolizumab treatments (75 mg intravenously every 4 weeks, or 100 mg subcutaneously every 4 weeks) were compared to placebo (13). It was observed that both mepolizumab therapies significantly reduced the frequency of asthma exacerbations and improved post-bronchodilator FEV1 values compared to baseline; however, the effect of mepolizumab on remission was not investigated in this study (13). In the Open-label Long Term Extension Safety Study of Mepolizumab in Asthma Subjects (COLUMBA) study, it was reported that 33% of the patients did not experience exacerbation after an average of 3.5 years of mepolizumab treatment (15). In a recent observational multicenter retrospective study, the 12-month remission rates of mepolizumab treatment in severe asthmatic patients were investigated along with factors affecting remission (12). The percentage of patients in complete remission was reported as 30.12% among mepolizumab recipients (12). In a retrospective study, response to mepolizumab treatment was detected in 92.9% of patients (11). Eger and colleagues investigated treatment response and factors affecting treatment response over a 2-year period in patients with severe eosinophilic asthma receiving anti-IL-5 therapy. After 2 years of therapy, 14% of patients were defined as "super responders", 69% "partial responders", and 11% "non-responders" (14).

It is clear from aforementioned literature that the remission rates obtained with biological agents can vary considerably depending on the biological agent used, the patient population, and the accepted definition of remission. Apart from these, independent variables affecting remission rates are another subject of interest. Our results showed that having a higher FEV1% predicted value at baseline was the sole parameter independently associated with both 12-month and 36-month remission. In the study of Eger *et al.*, those who were "super-responders" to anti-IL-5 therapy were defined to have shorter asthma duration and higher FEV1. Super-responders tended to have adult-onset asthma, no nasal polyps, and lower BMI (14). Higher eosinophil counts or higher exacerbation rates have been presented as factors predicting super-response to anti-IL-5 therapy in some studies that defined super-response as reduction of exacerbations or decreased use of oral corticosteroids (29, 30). In a retrospective study, key features associated with "responder" and "super-responder" status to mepolizumab were found to be the presence of nasal polyposis, lower baseline score from the Asthma Control Questionnaire (ACQ)-6, lower BMI, and using lower oral prednisolone dosage at baseline (11). In the study by Harvey *et al.*, higher eosinophil and older age at asthma onset predicted better ACQ-5 results after receiving mepolizumab, while being male or having a BMI of ≥30 were associated with lower results (24). In the PROSPERO study, it was noted that responders had baseline blood eosinophil levels greater than or equal to 300 cells/mL (10). In addition, in studies with other biologic agents, variables such as higher eosinophil (29-33) and basophil counts (34), a history of more frequent exacerbations (29, 32), worse baseline lung function (16, 31, 32, 35, 36), use of oral corticosteroids (37) and nasal polyposis (37) have been associated with better clinical remission rates.

The main goal of current asthma therapy is to control airway inflammation and minimize symptoms. At present, there is no effective treatment available to address the chronic alterations in airway remodeling and their impact on lung function. As the majority of previous studies assessed disease control rather than remission, it is difficult to accurately determine the efficacy of biological agents in achieving remission, particularly in relevance to prior research (23). This requires a thorough understanding of the pathophysiology of asthma remission and airway remodeling, supplemented by necessary tissue-level or cellular investigations. Data obtained from the present study suggest that biological agent therapy in patients with severe asthma achieves considerably high remission rates at 12 months and 36 months. However, the detection of a higher chance of remission in patients with better lung function at baseline suggests that more effective treatment approaches need to be developed for patients with severe asthma that have poor pulmonary function. However, there is still a need for comprehensive studies investigating predictors of optimal response to biologic therapy.

One of the strengths of our study is the investigation of two different biological. The second is the investigation of both 12-month and 36-month clinical remission rates of these agents.

In most clinical studies, follow-up was limited to 12 months or less (10-12). Third, the factors affecting both 12-month and 36-month clinical remission rates with the extensive baseline characterization of the patients were investigated. However, the following limitations should be considered when interpreting the results of the study. It is a single-center study with relatively few participants, more so for the analyses of 36-month remission. Therefore, the generalizability of the results is limited. Due to the retrospective design, complete remission rates could not be obtained since this would necessitate prospective follow-up. Of the patients' phenoendotypic characteristics, only eosinophilic or allergic status was included in the study.

Other endotypic and phenotypic characteristics may affect clinical remission rates; however, the current study does not account for these factors. Since the use of agents other than omalizumab and mepolizumab are not yet approved in our country, the present study reports data for only these two agents, and therefore, the results are relevant in this context. Although criteria for defining clinical remission, such as improvement of symptoms, absence of exacerbations and the need for oral steroids, and spirometric improvement are well defined, cut-off values to define spirometric improvement are not clearly defined. Since this study included patients with severe asthma, we did not set a criterion for spirometric improvement (such as FEV1 % predicted value exceeding 80%), which has been used in some previous studies (38). Instead, we used the following criterion: more than 10% improvement in FEV1 % predicted value, which has also been suggested in prior research (4). This ambiguity makes it difficult to clearly define clinical remission and to compare our findings with other studies.

In conclusion, biological agents appear to provide significant clinical remission rates in severe asthma. However, due to the fact that higher FEV1% predicted is associated with higher likelihood of remission, there is an apparent need for more effective therapies in patients with poor pulmonary function at baseline. The data on this subject so far are from clinical studies. The present study is retrospective and thus reflects real life.

Fundings

None.

Contributions

KA: conceptualization. SY, KA, GTVS, ÖA, OT, HÇT, GKB, SNB, ŞD: methodology, data curation , writing – review & editing. SY: formal analysis; KA, SY: writing – original draft.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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The impact of a drug allergy label in an internal medicine ward

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Key words

Drug allergy; antibiotic allergy; self-reported allergy; allergy cost; allergy impact.

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Impact statement

A considerable number of patients had a self-report of drug allergy on their medical records, which entails difficulties on their clinical management, and contributes to increase the cost of their treatment.

Summary

Background. *Drug hypersensitivity reactions are presumably immune-mediated reactions that cause reproducible signs and/or symptoms. Overdiagnosis of drug allergy, frequently self-reported, is common and carries significant limitations. We intended to analyze the frequency and impact of drug allergy in hospitalized patients.* ***Methods.*** *A retrospective study was conducted in an internal medicine ward at a tertiary hospital in Portugal. All patients with a drug allergy report admitted within a 3-year period were included. Data were collected from their electronic medical records.* ***Results.*** *We found that 15.4% of patients had a report of drug allergy, with antibiotics being the most common (56.4%), followed by non-steroidal anti-inflammatory drugs (21.7%) and radiocontrast media (7.0%). The allergy report affected the clinical approach of 14.5% of patients by motivating the use of second-line agents, or the eviction of necessary procedures. The usage of alternative antibiotics entailed a cost increase of 2.4 times. There were 14.7% of patients to whom the suspected drug was administered: 87.0% tolerated and 13.0% developed a reaction. Only 1.9% were referred to our Allergy and Clinical Immunology Department and proceeded in their allergy study.* ***Conclusions.*** *In this study, a considerable number of patients had a drug allergy label on their records. This label contributed to an increase in the cost of treatment, or the avoidance of necessary exams. However, disregarding an allergy record may lead to potentially life-threatening reactions that proper risk assessment could avoid. Further investigation should always be part of the follow-up routine of these patients, and better articulation between departments should be encouraged.*

Introduction

Adverse drug reactions (ADRs) are unintended and potentially harmful drug events that occur at doses frequently used in clinical practice (1). Drug hypersensitivity reactions (DHR) are a type of ADR that is presumed to be immune-mediated and causes reproducible signs and/or symptoms (1) that can be life-threatening, may require or prolong hospitalization, and may impose changes in subsequent therapy (2). They account for 20% of ADRs and are reported in approximately 8% of the general population (3).

DHRs can be divided into immediate reactions, usually occurring within 1 to 6 hours after drug administration, and often presenting with urticaria, angioedema, nasal and ocular pruritus, sneezing, bronchospasm, hypoxemia, hypotension, vomiting, abdominal pain; or nonimmediate reactions, which may start several hours or even days after drug administration and usually present with cutaneous symptoms, such as urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis or severe cutaneous adverse reactions (toxic epidermal necrolysis, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms) (2, 4).

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Diagnosis is based on medical history, clinical manifestations, and *in vivo* or *in vitro* tests (2). However, overdiagnosis of a drug allergy is common, usually self-reported by patients, and/or incorrectly mistaken for other ADRs. This can become an important limitation for treatments, leading to the use of second-line agents that can be less effective, more expensive, and associated with more side effects (1).

This study aims to evaluate and characterize the frequency of drug allergy in hospitalized patients, and its impact on the patient's treatment.

Materials and methods

A retrospective study was conducted in an Internal Medicine ward, at a tertiary referral center in Lisbon, Portugal. All adult patients admitted between January 2018 and December 2020 with a drug allergy report on their records were included.

The variables gender, age, personal history, drug allergy history, current and previous treatments, clinical evolution during hospitalization, and follow-up after discharge were analyzed. Data were collected from electronic records from both medical and nursing staff.

A complete history of past drug allergy events was considered when there was information about the drug administered, the onset of reaction (immediate if the terms "immediate" or "minutes after" were present on the records, or nonimmediate for reactions described as "late", "several hours" or "days"), and the symptoms developed. Anaphylaxis was considered when there was a report of an immediate reaction with at least two systems involved.

A descriptive statistical analysis was conducted on the data collected. Cost analysis of antibiotic treatment was performed by comparing first-line agents that could have been employed *versus* the alternative treatment and multiplying by the number of days of use. The cost of each antibiotic was deducted from our hospital pharmacy form. This study was conducted following the approval of the Ethics Committee (CES 1052/2021).

Results

Population

Of a total of 3,532 admissions over the 3-year period, 3,046 patients were screened, and 470 (15.4%) were selected for having a drug allergy record. Most patients were female (n = 276, 58.7%) with a median (P25-75) age of 75 (63-83) years.

Drug characterization

The electronic record of drug allergy was registered in 51.7% (n = 243) of patients by the medical staff, and in 84.5% (n = 397) by the nursing team. History of allergy to antibiotics was present in 56.4% (n = 265) of patients, to non-steroidal anti-inflammatory drugs (NSAIDs) in 21.7% (n = 102), and to radiocontrast media (RCM) in 7.0% (n = 33). Further details of the suspected agents are represented in **table I**.

Table I *- Overview of drugs allergies reported on patients' electronic medical records.*

Drug	Total (n)	Relative %†	Absolute %‡
Antibiotics	265	56.4	8.7
Penicillins	209	44.5	6.9
Trimethoprim/ sulfamethoxazole	31	6.6	1.0
Quinolones	21	4.5	0.7
Cephalosporins	11	2.3	0.4
Macrolides	10	2.1	0.3
Others	16	3.4	0.5
NSAIDs	102	21.7	3.3
Salicylic acid	37	7.9	1.2
Metamizole	19	4.0	0.6
Ibuprofen	13	2.8	0.4
Diclofenac	10	2.1	0.3
Acetaminophen	9	1.9	0.3
Selective Cyclooxygenase 2 Inhibitor	8	1.7	0.3
Naproxen	5	1.1	0.2
Others	5	1.1	0.2
Radiocontrast media	33	7.0	1.1
Antihypertensive drugs	23	4.9	0.7
Angiotensin converting enzyme inhibitor	11	2.3	0.4
Others	16	3.4	0.5
Antiseptic	17	3.6	0.6
Povidone-iodine	15	3.2	0.5
Others	2	0.4	0.1
Opioids	16	3.4	0.5
Tramadol	16	3.4	0.5
Xanthine-oxidase inhibitors	10	2.1	0.3
Allopurinol	10	2.1	0.3
Others	84	17.9	2.8

Some patients had a record of allergy to more than one drug in the same class; †relative frequency in the 470 patients with a drug allergy label; ‡absolute frequency in the 3,046 patients admitted to the internal medicine ward during this time-period.

The most common drugs involved were penicillins, followed by salicylic acid, and radiocontrast media. In 14.5% (n = 68) of patients, there was a drug allergy report regarding more than one drug class. In 17.9% (n = 84) of patients, there were reports of administration of the suspected drug within the hospital setting without developing any adverse reaction.

Reaction characterization

The timing of reaction was described in 50.2% (n = 236) of the records, with immediate reactions being the most common (n = 199, 84.3%). Mucocutaneous manifestations were the most frequently reported (n = 201, 85.2%), followed by respiratory symptoms (n = 29, 12.3%) (**table II**). There were 18 reports of anaphylaxis, 4 of them without mucocutaneous involvement.

Table II - *Characterization of manifestations according to time of onset.*

Manifestations (n = 236)	Immediate n (%)	Non immediate n (%)
Mucocutaneous	152 (64.4)	35 (14.8)
Respiratory	15 (6.4)	-
Cardiovascular	6 (2.5)	-
Gastrointestinal	8 (3.4)	2 (0.8)
Anaphylaxis	18 (7.6)	-
Total	**199 (84.3)**	**37 (15.7)**

Implications on clinical practice

Changes in clinical management directly related to the drug allergy history were verified in 14.5% (n = 68): 76.5% (n = 52) received a second-line treatment agent, with most cases (n = 45) related to the use of alternative antibiotics (**table III**), and 23.5% (n = 16) were denied an exam or procedure, mostly due to the need of radiocontrast administration (n = 12). Regarding the group in which an alternative antibiotic was used, 28.9% (n = 13) had already received the culprit drug in previous hospital admissions and had developed no reaction. The median (P25-75) of days of use was 7 (3-10) days. This change entailed an increase in the cost of treatment of 2.4 times per patient, compared to the treatment with the drug in avoidance (35.96 *vs* 14.94 euros per patient treated).

The suspected drug was administered in 14.7% (n = 69) of patients: 78.3% (n = 54) were antibiotics, 10.1% (n = 7) NSAIDs, 2.9% (n = 2) RCM, 2.9% (n = 2) bronchodilators and 5.8%

Table III - *Antibiotics avoided and respective alternative.*

Avoided	Alternative used	Total (n)
Penicillins	Cephalosporins	19
Penicillins	Quinolone	9
Penicillins	Piperacillin/tazobactam	5
Penicillins	Carbapenem	3
Penicillins	Lincosamide	3
Penicillins	Macrolide	2
Cephalosporins	Piperacillin/tazobactam	1
Cephalosporins	Carbapenem	1
Trimethoprim/ sulfamethoxazole	Naphthoquinone	1
Glycopeptide	Oxazolidinone	1
Total		**45**

Table IV - *Reactions' description after re-administration of suspected drugs and comparison with previous event.*

Reported culprit drug	Previous reaction	Symptoms	Drug administered	Current reaction	Symptoms
Penicillins	Immediate	Mucocutaneous Respiratory	Amoxicillin	Immediate	Cardiovascular Respiratory
Penicillins	Immediate	Mucocutaneous	Amoxicillin	Immediate	Mucocutaneous
Penicillins	No Record	No Record	Piperacillin/tazobactam	Nonimmediate	Mucocutaneous
Cephalosporins	Nonimmediate	Mucocutaneous	Ceftazidime	Nonimmediate	Mucocutaneous
Trimethoprim/ sulfamethoxazole	Nonimmediate	Mucocutaneous	Trimethoprim/ sulfamethoxazole	Nonimmediate	Mucocutaneous
Acetaminophen	Immediate	Mucocutaneous	Acetaminophen	Immediate	Mucocutaneous
Ibuprofen	Immediate	Mucocutaneous	Naproxen	Nonimmediate	Mucocutaneous
RCM	Immediate	Mucocutaneous	RCM	Immediate	Mucocutaneous
Ipratropium bromide	Immediate	Mucocutaneous	Ipratropium bromide	Immediate	Mucocutaneous

RCM: radiocontrast media.

(n = 4) other drugs. In this group, a complete record of past events was present in 49.3% (n = 34) of these patients, with 29 reporting immediate symptoms, and 5 describing nonimmediate reactions. After administration of the suspected drug, 87.0% (n = 60) of the patients had no reaction and 13.0% (n = 9) presented a reaction assumed, by the attending physician, as a hypersensitivity reaction, one of which was anaphylaxis. The reactions' description is presented in **table IV**.

Follow up

After hospital discharge, 1.9% (n = 9) of patients were referred to our Allergy and Clinical Immunology Department for an allergy study. Of these, six suspicions were excluded after skin and provocation tests, one was assumed to be angioedema secondary to angiotensin-converting enzyme inhibitor, and two missed their appointments.

Discussion and conclusions

We found that 15.4% of patients had a record of drug allergy, which is higher than the frequency reported in the general population (approximately 8%) (1), and in a previous study conducted in Portugal regarding self-reported drug allergy (7.8%) (5). This overdiagnosis might be explained by the fact that the population studied refers to inpatients, who are probably more exposed to drugs than the general population and, as such, more prone to develop reactions that can be misinterpreted as a DHR. Another factor that might have contributed was that it is based on self-reports and previous records, that may contain errors or incomplete data. DHRs are often over diagnosed, due to the incorrect use of the term "allergy" in the presence of manifestations possibly from other causes, such as viral infections, expected ADRs, and other conditions nonrelated to drug allergy (2).

Our study showed a female predominance (58.7%), as published in the literature (1, 3, 6).

We found a clear difference between medical and nursing records, with more allergy reports registered by the nursing team (84.5% *vs* 51.7%). This difference might be explained by some hypothesis, namely: 1) the hospital admission is performed by nurses, who have the first contact with the patient, and collect a pool of information, such as previous drug allergies; 2) during the hospital stay, medication is administered by nurses, and patients may recall previous reactions to certain drugs and report them at that time; 3) some reactions reported by patients are not compatible with a DHR, which may lead the physician to omit them from their records more easily than the nurse. We found no other studies in the literature that addressed this aspect.

Regarding drug classes, we found that the most implicated group of drugs were antibiotics (8.7%), particularly beta-lactams, and NSAIDs (3.3%), which is very similar to a recent study where 5.8% of patients self-reported allergy to antibiotics, and 1.5% to NSAIDs (7).

In our population, the most frequent drug allergy report was to penicillins, with a frequency of 6.9%. Recent studies report a prevalence of 5 to 16% in hospitalized patients (8). Even though our result is within this range, it may not correspond to the number of patients with true penicillin allergy, since 70% of subjects with a history of allergy to beta-lactams are confirmed not allergic when submitted to proper tests (4).

NSAIDs-hypersensitivity reports were slightly higher when compared with the general population (3.3% *vs* 2% respectively) (9), which might be related to the fact that the study was conducted with inpatients.

Regarding RCM hypersensitivity (1.1%), our results are in line with the reported frequencies of DHRs in 0.5 to 3% of patients receiving nonionic RCM (10). The same applies to multiple drug class allergy reports (2.2%), which are within the estimated values currently published (1 to 10% of patients may have DHRs to distinct and non-cross-reactive drugs) (6).

Immediate reactions and mucocutaneous manifestations were the most frequently reported, in accordance with current literature, where mucocutaneous is the most described system to be affected during DHRs (1). We detected that about half of the records contained incomplete data, regarding the time of onset and symptoms developed during the suspected reaction, which may compromise risk assessment. This description is vital to differentiate between immediate reactions, mostly associated with an IgE mechanism *versus* nonimmediate reactions, commonly through a T-cell-dependent mechanism (6, 11, 12). The characterization of signs and symptoms developed, as well as the therapeutic approach, also contribute to improve risk assessment. However, healthcare professionals often register incomplete, or incorrect information when recording a drug allergy in electronic medical records, leading to difficulties in the decision to administer or avoid the drug in question (13).

Patients with an antibiotic hypersensitivity history are often treated with second-line antibiotics, associated with higher risks and costs (8, 13). We verified that the allergy labels modified the antibiotic prescribing habits, increasing over 2.4-fold the expected cost of treatment (35.96 *vs* 14.94 euros per patient). Similar studies have also documented this economic burden on healthcare costs: Li *et al*. reported that the use of second-line antibiotics, in patients with penicillin allergy labels, was responsible for an increase between 1.82 to 2.58 times the expected cost of treatment (14). Picard *et al*. demonstrated an increase of 74% in the cost of treatment of inpatients where an alternative antibiotic was used, due to a history of penicillin allergy (15). Bermingham *et al*. also found that, in patients with sepsis, the cost of alternative antibiotics was 2.61 times higher, when a label of penicillin allergy was present (16). These data demonstrate the importance of develop-

ing delabelling strategies, since they will allow patients to receive first-line treatments, and help to reduce healthcare expenses.

More than one-third of our patients, labeled with RCM allergy, were denied an exam requiring RCM administration. On the other hand, of the two patients who were submitted to exams with RCM regardless of their label, one reacted and the other did not. Neither had a description of the RCM administered. Hypersensitivity reactions to RCM are a considerable challenge in clinical practice: the exact name of the agent used is often unknown, and the description of the adverse reaction usually lacks detail. This leads to difficulties in the correct risk assessment and generates uncertainty, resulting in the avoidance of certain procedures (10, 17). Drug provocation test is the gold standard for drug allergy diagnosis (2). The demonstration of tolerance, after the suspected event is enough to remove the allergy label (18). We verified that 17.9% of patients with current allergy labels had already received, and tolerated the drug in question in the hospital setting, allowing the exclusion of the suspected allergy. However, this label was not removed and was still present on their records. This resulted in unnecessary avoidances in 28.9% of the patients, to whom an alternative antibiotic was administered, and might have been prevented if previous records were consulted, or if the label had been removed. Prompt exclusion of this diagnosis, without a careful and experienced evaluation, may carry danger for the patient, as seen in the one that suffered anaphylaxis after receiving the suspected drug. The other patients, to whom the drug was administered and did not react, may have the allergy label removed so that it does not harm future admissions. This highlights the importance of complete and correct medical records.

Allergy de-labeling, particularly for penicillins has been demonstrated to be cost-effective *versus* the use of second-line agents (18, 19). To achieve that goal, proper referencing is crucial. However, in our population, it is worth mentioning the very low number of patients referenced for allergy evaluation after hospital discharge (n = 9, 1.9%). This poor referencing may have repercussions on future admissions. Some of the reports of suspected allergies can be confirmed, or excluded with appropriate testing, performed by an experienced allergist, either during the hospital stay or after discharge, which would reduce the uncertainty when choosing future therapeutic options for those patients. A better articulation between departments should be encouraged to improve patient management and reduce the healthcare burden of drug allergy labels.

The strength of our study is that it is a descriptive analysis of a large specific population. This might help to provide better estimates of frequency of drug allergy in this group of patients and contribute to improve their management. It also raises awareness of the negative impact of these labels, and the increase in costs that they represent.

A major limitation of our study is that it depends on self-reports and previous records, which makes us susceptible to errors in the interpretation of episodes, incorrect records, or incomplete data. Another limitation is that it is not a multicentric study, which may not reflect general practices. It would be of interest to conduct similar studies in other centers to compare procedures and adopt better future practices.

In conclusion, a considerable number of patients have a drug allergy label on their electronic medical records. As expected, antibiotics and NSAIDs are the most reported. However, the previous reaction description is missing in about half of them, making a correct risk assessment difficult. This can result in unnecessary avoidances, with increasing complications and healthcare costs, or potentially harmful effects by administration of the suspected drug. A better articulation between departments and proper referencing and diagnosis should be part of the follow-up routine of these patients, contributing to improve both the clinical management and treatment costs in future admissions.

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Contributions

PC, GS, JO: conceptualization. PC, GS, MM: data curation. PC, GS, JO, PP: formal analysis. PC, GS, MM: investigation. PC, JO: methodology. ES, PP: project administration. JO, SR, ES, PP: supervision. JO, PP: validation. PC, GS, MM: visualization. PC, GS, MM: writing – original draft. JO, SR, ES, PP: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Alana Xavier de Almeida[1], Travis Satnarine[1], Jennifer Gebbia[2], Hugh A. Sampson[3], Gary Kleiner[2], Melissa Gans[2]

IgE-mediated flaxseed allergy in non-atopic toddler polysensitized to tree nuts but tolerating other seeds

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Key words

IgE-mediated allergy; anaphylaxis; flaxseed allergy; flaxseed; urticaria.

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To the Editor

flaxseed use has been increasing worldwide for its health benefits of high content of omega-3 fatty acids and laxative effect (1, 2). While limited cases of flaxseed hypersensitivity have been described, most of them describe anaphylactic reactions in adult patients with associated atopic disease (1-5). This report presents a case of IgE-mediated allergic reaction to flaxseed in a non-atopic toddler.

An 18-month-old male patient developed a raised erythematous pruritic rash throughout his face and chest about 20 minutes after consuming a packet of oatmeal with premixed flaxseed. He consumed approximately 1,800-2,200 mg of flaxseed protein per manufacturer. The event self-resolved within 4 hours. Mother reported that she consumed flaxseed protein shakes daily during her pregnancy and lactation. However, this was the first time the patient orally ingested flaxseed.

The patient did not have a history of atopic disease. Skin prick test was performed at 24 months revealing positive peanut (11 mm wheal), walnut (13 mm wheal), cashew (7 mm wheal), hazelnut (5 mm wheal), and fresh flaxseed (10 mm wheal) with saline (0 mm wheal) and histamine (6 mm wheal). Evaluation also included measurement of serum IgE levels (**table I**). Based on history and test results, a diagnosis of IgE-mediated reaction to flaxseed was made.

The patient had never consumed: peanut, almond, hazelnut, Brazil nut, cashew, pistachio, pecan, walnut, lupine seed, chestnut, chia seed, poppy seed, hemp seed, lychee nut, or macadamia nut. He had orally tolerated without reaction: sesame seed, pumpkin seed, pine nut, sunflower seed, lentil, black bean, chickpea, green pea, and soy. He did tolerate one entire granola bar containing approximately 122 mg of flaxseed protein per manufacturer which is less than 10% of flaxseed protein the patient reacted to.

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Table I *- Laboratory results.*

Laboratory testing	Result (19 months)	Result (31 months)	History
Total IgE	595 kU_A/L	396 kU_A/L	N/A
Flaxseed IgE	15.20 kU_A/L	47.50 kU_A/L	Reaction
Peanut IgE	52.00 kU_A/L	13.00 kU_A/L	Never consumed
Ara H1 IgE	2.58 kU_A/L	0.33 kU_A/L	Never consumed
Ara H2 IgE	49.30 kU_A/L	7.92 kU_A/L	Never consumed
Ara H3 IgE	1.49 kU_A/L	0.93 kU_A/L	Never consumed
Ara H8 IgE	< 0.10 kU_A/L	< 0.10 kU_A/L	Never consumed
Ara H9 IgE	4.12 kU_A/L	1.11 kU_A/L	Never consumed
Almond IgE	12.70 kU_A/L	8.80 kU_A/L	Never consumed
Hazelnut IgE	11.40 kU_A/L	11.70 kU_A/L	Never consumed
Cor a1 IgE	< 0.10 kU_A/L	1.92 kU_A/L	Never consumed
Cor a8 IgE	0.67 kU_A/L	0.34 kU_A/L	Never consumed
Cor a9 IgE	11.70 kU_A/L	10.5 kU_A/L	Never consumed
Cor a14 IgE	0.40 kU_A/L	0.34 kU_A/L	Never consumed
Brazil Nut IgE	7.08 kU_A/L	5.88 kU_A/L	Never consumed
Ber e1 IgE	< 0.10 kU_A/L	0.52 kU_A/L	Never consumed
Cashew Nut IgE	10.50 kU_A/L	7.60 kU_A/L	Never consumed
Ana 03 IgE	5.00 kU_A/L	0.41 kU_A/L	Never consumed
Pistachio IgE	15.80 kU_A/L	9.75 kU_A/L	Never consumed
Pecan Nut IgE	7.15 kU_A/L	2.42 kU_A/L	Never consumed
Walnut IgE	44.30 kU_A/L	7.20 kU_A/L	Never consumed
Jug r1 IgE	38.10 kU_A/L	5.67 kU_A/L	Never consumed
Jug r3 IgE	3.79 kU_A/L	1.02 kU_A/L	Never consumed
Soybean IgE	N/A	3.52 kU_A/L	Tolerates
Macadamia Nut IgE	4.89 kU_A/L	N/A	Never consumed

IgE: Immunoglobulin E; kU_A/L: kilounits per liter; N/A: not applicable.

A direct oral challenge for flaxseed and other nuts was offered but not performed per parents' preference. A diet avoiding flaxseed was recommended, but the patient was allowed to consume products containing trace amounts.

This is the first reported case to our knowledge of a toddler with an immediate IgE-mediated reaction to flaxseed with positive flaxseed-specific IgE in the setting of polysensitization to other seeds and nuts. Interestingly, the flaxseed-specific IgE is very high (15.20 kU_A/L, 47.50 kU_A/L) with a mildly elevated total IgE. The patient does not have any atopic conditions explaining an elevated IgE beyond food allergies. We do not have sufficient population data to determine the positive predictive value of a positive specific flaxseed IgE but our patient's laboratory values would suggest that flaxseed specific IgE in flaxseed allergic individuals runs higher than other seeds and tree nuts.

We question if this patient is truly allergic to other related foods such as peanuts and other seeds for which he has positive IgE testing. The flaxseed IgE is higher than the other food-specific IgE values, making us suspect that this is the prominent allergen and the other positive tests may only represent sensitization and not true allergy, although IgE values are food specific and cannot be directly compared. Another case report in an adult patient is consistent with our theory that flaxseed allergy might have positive sensitization to other nuts and seeds without true allergy (2, 6). Our patient reacted to first known oral ingestion of flaxseed, suggesting that he was previously sensitized. We hypothesize that he was sensitized cutaneously as an infant from his mother who consumed flaxseed smoothies regularly (7).

Given the use of flaxseed is increasing, the number of allergic reactions associated with this seed will likely increase (3). Allergists need to be aware of flaxseed allergy and more research needs to be performed on cross-reactivity among nuts, legumes, and other seeds, and positive predictive values of flaxseed specific IgE established.

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Contributions

AXA, MG: conceptualization, writing – original draft, writing – review & editing. TS: writing – original draft, writing – review & editing. JG, HAS, GK: writing – review & editing.

Conflict of interests

MG has served as a consultant for GRG Health, Pharming Healthcare, LDA Research, and LEK GmbH; receives royalties from Elsevier; is a grant recipient from Pfizer; and performs research with Novartis, Regeneron, and DBV. HAS has received consulting fees from N-fold, LLC, DBV Technologies, Abbvie, and Siolta Therapeutics; receives royalties from Elsevier; is a grant recipient from the National Institute of Allergy and Infectious Disease and Allergenis. Other authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Salt dependent aquagenic urticaria: nine new cases and proposal for a diagnostic work-up

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Key words

Aquagenic urticaria; salt-dependent aquagenic urticaria; AquaU; SDAU; diagnostic workup.

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To the Editor,

AquaU is an uncommon form of Chronic Inducible Urticaria (CIndU) characterized by whealing at the site of contact of the skin with water, regardless of its temperature, within minutes of exposure (1). A salt-dependent subtype of aquagenic urticaria (SDAU) has been described that could represent either a distinct variant or part of a severity spectrum of AquaU (2). We herein present nine new patients whose characteristics are consistent with SDAU and we suggest a standardized diagnostic workup for AquaU.

We retrospectively reviewed the data of nine female patients (mean age ± SD, 26.78 ± 12.36 years) diagnosed with SDAU in our dermatology department from 2016 to 2022. Only one had a family history of similar symptoms and 7/9 had an atopic background. These patients reported highly pruritic urticarial rashes triggered by sea bathing; some of them also reported different degrees of reactivity to tap water, swimming-pool water and sweat. They underwent the diagnostic workup shown in **figure 1**. The results are summarized in **table I**.

AquaU is considered rare, but its true prevalence is unknown, and it has been suggested that mild cases might be frequent and underestimated (2). It is predominant in young female patients and most cases are sporadic, although a classification into familial AquaU and acquired AquaU has been proposed (3). In addition to fresh and sea water, other rarely reported aqueous triggers include rain, snow, tears and saliva. Wheals commonly occur in localized body areas (mainly trunk and lower face/neck) even in case of exposure of the whole body to water (3, 4). They develop within minutes of water contact and rapidly resolve after its cessation. The pathogenesis of AquaU is a mystery. The different hypothesis so far suggested include the generation of either a toxic substance or of an auto-allergen derived from water-soluble components present in

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Table I *- Clinical characteristics, type of water triggers, results of water challenge tests and treatment in nine patients with SDAU.*

						Triggers				Timing		Localization	Water challenge tests			Response to treatment	
Gender/ age (yy)	Atopic background	Total IgE (normal range 0.0-100.00 KU/l)	Familial cases	Other CindUs	AU duration (yrs)	Sea water (sea bathing)	Tap water	Swimming pool water	Sweat or other aqueous triggers (*e.g.* rain)	Latency of wheals	Duration of wheals	Body areas affected	3.5% NaCl: soaked pads on specific areas	Tap water: soaked pads on specific areas	Tap water: full body	AntiH1 standard dose	Other drugs
F/30	Allergic rhinitis	31.6	No	No	4	Yes	Yes*,**	Yes	Sporadically sweat	10'	30-60'	Mandibular area, neck, chest	+	Neg	10' bath ++	Partial response	None
F/24	Allergic rhinitis	130.0	No	No	5	Yes	Yes**	No	Sporadically sweat	10'	60'	Mandibular area, neck, chest, upper back, shoulders	+	Neg	15' shower ++	Good response	None
F/17	Allergic asthma	89.0	No	No	3	Yes	Yes*	No	No	15'	10'	Neck, décolleté, upper back	+++	++	Not performed	Poor response	None
F/57	No	47.8	No	Cold u.	2	Yes	No	Yes	No	15'	30'	Widespread	++	+/-	Not performed	Partial response	None
F/17	Allergic asthma	300.0	No	No	1	Yes	Yes*,**	No	Sporadically sweat	15'	30'	Mandibular area, neck, upper trunk	++	+	Not performed	Good response	None
F/19	Allergic rhinitis	150.0	No	No	3-4	Yes	Yes*	Yes	Sweat	10'	60'	Neck, décolleté, shoulders	+++	+	Not performed	Partial response	None
F/27	Allergic rhinitis and asthma	70.9	No	No	10	Yes	Yes*	Yes	No	10'	60'	Trunk and arms	++	+	Not performed	Poor response	None
F/29	No	45.6	Yes, mother	No	20	Yes	Yes*,**,***	Yes	No	10'	30-60'	Face, neck, décolleté, shoulders	+/-	Neg	15' shower ++	No treatment	None
F/21	Previous atopic dermatitis and allergic rhinitis	176.0	No	Dermographic urticaria	10	Yes	Yes*	Yes	No	10'	30'	Face, neck, décolleté, shoulders, lower limbs	+/-	Neg	10' shower ++	Partial response	Controlled by omalizumab

Triggers: *shower, **bath, *** face washing; U: Urticaria; Anti-H1: anti-histamines; none of the patients had systemic symptoms; all patients underwent full blood count, C-reactive protein, tests for anti-nuclear antibodies, C3-C4 and anti-thyroid antibodies with unremarkable results; all patients underwent an ice cube test for cold urticaria as described in the EAACI/ GA2LEN/EDF/ WAO consensus recommendations for CIndU; all patients underwent water challenge tests with tap water and with a 3.5% NaCl water solution (iso-osmolar with the Mediterranean Sea water) at room temperature, by means of soaked compresses applied for 20' to the body areas that they reported as more intensely affected by AquaU; four patients who reported urticaria from contact with both sea water and tap water but reacted positive to the local challenge with salty water only, underwent a full body tap water challenge test at home (bath or shower without any concomitant use of shower/bath products); the consequent skin reactions were documented by neat pictures taken by patients with their smartphones; intensity of positive reactions to water challenge tests: +/- patches of faint itchy erythema, + pruritus with few (1-4) tiny wheals surrounded by erythema,++ pruritus with 5 to 10 wheals surrounded by erythema, +++ intense pruritus with diffuse erythema scattered with more than 10 wheals.

Figure 1 *- Diagnostic workup of patients presenting with a history suggestive of aquagenic urticaria.*

Patient presenting with a history of fleeting itchy rashes triggered by skin contact with water
(for example, when taking a shower, bathing or swimming)

↓

General data

- **Gender** M F
- **Age**
- **Familial history of atopy** ☐No ☐Yes
- **Personal history of atopy** ☐No ☐Yes
  ☐Atopic Dermatitis ☐Respiratory Allergy ☐Food Allergy
  ☐Other (hymenoptera, type I drug allergy…)
- **Comorbidities** (thyroid diseases, gastrointestinal diseases, autoimmune diseases, others):
  ……
- **Coexistence of other urticarias** ☐No ☐Yes
  ☐Cold Urticaria ☐Symptomatic dermographism
  ☐Cholinergic Urticaria ☐Other CIndU ……
  ☐Chronic Sponteous Urticaria
- *AquaU was* ☐*the primary reason for consultation* ☐*a casual discovery while taking history for other problem. In particular, did the patient present with a request of patch testing for the suspicion of allergic contact dermatitis to cosmetic products such as shampoos or shower gels?* ☐No ☐Yes

AquaU specific data

- **Age at onset** **Duration (yy)**
  With time, signs and symptoms ☐have improved ☐have become worse ☐ have not changed
- **Family history of similar cases?** ☐No ☐Yes ☐mother ☐siblings ☐other ……
- **Types of water** (and related activities) **that trigger signs and symptoms**
  - **Tap water** ☐No ☐Yes ☐showering ☐bathing
    ☐washing face ☐washing hands
    ☐other (e.g. drinking water): ……
  - **Swimming pool water** ☐No ☐Yes ☐Not known
  - **Sea water (sea bathing)** ☐No ☐Yes ☐Not known
  - **Rain** ☐No ☐Yes
  - **Sweat** ☐No ☐Yes ☐always/often*
    ☐only when the skin is really wet with sweat
  - **Tears** ☐No ☐Yes
  - **Saliva** ☐No ☐Yes
  - **Other:** ……

** consider/test for cholinergic urticaria as possible differential diagnosis or comorbidity*

- **Signs and symptoms (skin)** ☐Itch ☐erythema ☐wheals ☐angioedema
- **Body areas affected** ☐face (lower) ☐face (all) ☐neck ☐upper chest ☐upper back
  ☐shoulders ☐abdomen ☐whole trunk ☐upper limbs
  ☐lower limbs ☐other specific: …… ☐generalized
- **Systemic symptoms** ☐No ☐Yes ☐respiratory distress/wheezing, ☐difficult swallowing
  ☐dizziness ☐syncope ☐other ……
- **Time of appearance of wheals after the start of water contact**
  ☐5′-10′ ☐10′-15′ ☐20′-30′ ☐>30′
- **Time of resolution of wheals after the end of water contact**
  ☐10′- 15′ ☐15′-30′ ☐30′-60′ ☐>60′
- **Are signs and symptoms influenced by the duration and amount of water contact?** for example
  are they more severe after swimming or after a long shower? ☐No ☐Yes ☐Not sure
  are they milder/resolve earlier if the water is wiped off soon after contact? ☐No ☐Yes ☐Not sure
- **Is the temperature of the water of any relevance?** ☐No ☐Yes * ☐Not sure*

** consider/test for cold urticaria or heat urticaria as possible differential diagnosis or comorbidities*

- **Was the problem ever treated with a standard dose of any antiH$_1$**
  ☐No ☐Yes, with
  ☐complete control ☐marked improvement ☐partial improvement ☐no improvement
- **Were higher doses of antiH1 tried?**
  ☐No ☐Yes, with
  ☐complete control ☐marked improvement ☐partial improvement ☐no improvement
- **Was the patient ever treated with Omalizumab?**
  ☐No ☐Yes, with
  ☐complete control ☐marked improvement ☐partial improvement ☐no improvement

Investigations

- Full blood count:
- C reactive protein:
- Total IgE:
- Anti-TPO antibodies:
- Other investigations (based on patient history):
  ……

Water Challenge Tests

Localized Water Challenge Tests (with tap water and salty water, in all patients)
By means of soaked cloths or towels applied, on opposite sides, for 20′ at room temperature

Body area tested
☐mandibular/peri-auricular zone and neck ☐neck and décolleté ☐upper arm and shoulder
☐upper back ☐chest ☐abdomen ☐thigh ☐other…….

Results

Tap water
Wheals and erythema
Neg +/- + ++ +++ Itch intensity 0------1------2-------3

Salty water (3.5% NaCl)
Wheals and erythema
Neg +/- + ++ +++ Itch intensity 0------1------2-------3

Full Body Water Challenge Test (with tap water, in selected patients)
for 15′, with lukewarm water without any concomitant use of shower/bath products
☐shower ☐bath

Results

Tap water
Wheals and erythema
Neg +/- + ++ +++ Itch intensity 0------1------2-------3

Were supplementary water challenge tests tailored on the patient's history performed to confirm a doubtful diagnosis? ☐No ☐Yes (specify):
……
……

All patients should undergo a localized water challenge test with both tap and salty water (3.5% NaCl), at room temperature, by means of well soaked cloths or towels applied, each on one side, to the specific body areas indicated by each patient as more likely to be reactive. The application should last for 20′.
Patients who do not react to the localized challenge tests should be asked to undergo, at home, a full body water challenge test, in the form of showering or bath immersion, for 15 minutes, with lukewarm tap water without any concomitant use of shower/bath products. The consequent skin reactions should be documented by clear pictures taken with their smartphones. Supplementary water challenge tests tailored on the patient's history should be performed whenever necessary to confirm a doubtful diagnosis.
The intensity of positive reactions can be scored as follows
+/- patches of faint itchy erythema
+ few (1-4) small wheals surrounded by erythema
++ 5 to 10 sparse wheals surrounded by erythema
+++ confluent erythema scattered with more than 10 wheals
The intensity of pruritus can be scored from 0 (absent) to 3 (very intense) with a simple visual scale

the sebum (5) or in the stratum corneum (6), respectively. The recently reported effectiveness of omalizumab in some patients suggests a role for circulating IgE (2, 7). Sudden changes in osmotic pressure around hair-follicles have also been advocated (3, 4, 8) and may account for SDAU. With the inclusion of the nine cases here described, the number of patients reported to react to salty water (42/118) accounts for 35.6% of total AquaU published cases (2-4, 7-10).

Based on our experience and on the characteristics described by other authors (8-10), many SDAU patients have an atopic background (16/27, 59%) and whealing frequently involves their lower face and neck (20/27, 74%). These associations are difficult to interpret. An altered skin barrier function in atopic patients and a high concentration of hair follicles in the mandibular area might play a role. Basically, the diagnosis of AquaU depends on a suggestive clinical history combined with a provocation test, the common method for which is to apply a cloth dampened with water at room temperature to the skin for 20 minutes, with an urticarial reaction indicating a positive test. We suggest that all patients with suspected AquaU should undergo local challenge tests with both tap water and salty water (NaCl 3.5%, iso-osmolar with sea water), as salty water may be more sensitive, and it may lower the threshold of response. If this observation of ours were confirmed, it would support the hypothesis that salinity is a relevant parameter for AquaU in general. Other water challenges, tailored on the patient's history, are sometimes necessary to clarify the diagnosis (4) (**figure 1**).

In conclusion, we propose a standardized diagnostic workup (**figure 1**) to be applied in all suspected cases of AquaU to harmonize future reports of the disease.

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Contributions

RG: conceptualization, data investigation, methodology, project administration, supervision, validation, visualization, writing - original draft, writing - review & editing. IT: data curation, methodology, project administration, software, visualization, writing - original draft, writing - review & editing. GG: methodology, software, validation, visualization, writing - original draft, writing - review & editing. RC: software, validation, visualization, writing - review & editing. GM: data curation, investigation, methodology, visualization, writing - review & editing. AP, EC: supervision, validation, visualization, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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