Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Ardesi F, Delvino P, Vanetti M, et al. **Addressing unmet needs in uncontrolled asthma through a specialized severe asthma center**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.3908

Submitted: 23-01-2026
Accepted: 10-07-2026

Addressing unmet needs in uncontrolled asthma through a specialized severe asthma center

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Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: not applicable.

Funding: this work was partially supported for Istituti Clinici Scientifici Maugeri, by the "Ricerca Corrente", funding scheme of the Italian Ministry of Health. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: OpenAI's ChatGPT image generation tool was used to generate Figures 1 and 2. The use of generative artificial intelligence is also explicitly disclosed in the corresponding figure captions.

Abstract

Severe asthma represents a clinically challenging proportion of the asthma population, characterized by persistent symptoms, frequent exacerbations, and a higher healthcare burden. To address the complexity of uncontrolled disease, specialized severe asthma clinics have emerged as key models for delivering precision medicine through multidimensional assessment and tailored interventions. This paper describes the organization, clinical approach, and multidisciplinary framework of a tertiary Severe Asthma Centre established in Northern Italy in 2017. The center integrates prioritized outpatient access with a structured day-hospital program (Complex Outpatient Macro Activity, MAC), enabling accelerated diagnostic work-up, comprehensive phenotyping/endotyping, and repeated educational interventions. Central elements include confirmation of diagnosis, assessment of type 2 inflammatory biomarkers (FeNO, IgE, blood and sputum eosinophils), evaluation of airway inflammation, and systematic identification of pulmonary and extrapulmonary treatable traits. A broad multidisciplinary network supports the management of comorbidities such as allergic rhinitis, chronic rhinosinusitis, hypereosinophilic disorders, allergic bronchopulmonary aspergillosis, metabolic and endocrine complications, gastroesophageal reflux disease, and vocal cord dysfunction. Pulmonary rehabilitation is integrated as an adjunctive intervention, particularly for patients with severe disease. Our severe asthma clinic implements precision medicine and the treatable traits approach in clinical practice to optimize outcomes, rationalize biologic therapy use, and reduce glucocorticoid exposure. Future perspectives include expansion toward a "united airways disease" clinic, integrating upper and lower airway management to further improve care for complex inflammatory airway diseases.

Key words: severe asthma, multidisciplinary management, biomarkers.

Introduction

Asthma is a common chronic respiratory disease, typically characterised by airway inflammation Nowadays, it remains a major global health concern, affecting approximately 300 million of people worldwide [1]. The disease may significantly impact patients' quality of life and imposes a considerable burden on healthcare systems [2]. A major contributor is due to the severe asthma phenotypes, which account for approximately 5–10% of the asthma population and are associated with greater symptom severity, frequent exacerbations, and increased healthcare resource utilisation [1,3].

Asthma is a complex and heterogenous condition, and while most asthma patients can effectively manage their condition in primary care, a subset of individuals with uncontrolled disease may require a specialized management to achieve optimal control [4-7]. In response to these growing needs, numerous specialized clinics have been set-up in recent years [4,8-10].

Severe asthma clinics have already demonstrated their key role in improving patient outcomes and disease management by offering a multidimensional assessment [11] and specialist evaluation [12]. Indeed, these services integrate differential diagnosis, pheno-endotyping, multidisciplinary approaches, educational interventions, treatment optimization, tailored treatment strategies and precision medicine [6,7,13-18]. Moreover, some of them contribute also to medical training and research, while ensuring better access to advanced treatments and supporting health care services [4,9].

The aim of this review is to characterize our centre's organizational model and to provide an overview of the main multidisciplinary assessments needed in a severe asthma centre.

Our center and its challenges in asthma management

A Severe Asthma Centre was established in 2017 at the Respiratory Unit of Istituti Clinici Scientifici Maugeri, Tradate, in Northern Italy. The centre was built on prior clinical experience and established organizational models [8,19]. Over subsequent years, several organizational and clinical implementations were introduced to optimize asthma management and improve patient outcomes. These adaptations were driven by evolving clinical evidence, the increasing complexity and volume of referrals, and, in particular, the widespread introduction of biologic therapies, which required more comprehensive and specialized patient evaluations. Our service provides a comprehensive approach, ranging from diagnosis confirmation to multidisciplinary evaluation (Figure 1). Patients referred for uncontrolled asthma are not

limited to those previously evaluated by hospital pulmonologists, but come through multiple referral pathways, including general practitioners, specialist outpatient clinics - such as ENT, immunology, allergology and dermatology - internal medicine and pulmonology wards. This heterogeneous referral network, developed through long-standing experience in asthma care, reflects the clinical complexity of uncontrolled asthma and the need for a structured pathway able to integrate respiratory, allergic, immunological and extrapulmonary assessments.

Ad-hoc organisation and educational program

Our approach is based on a daily out-patients clinic and/or a structured day-hospital program run by a multidisciplinary team named as Complex Outpatient Macro Activity (MAC). Furthermore, multi-specialist's consultation and pulmonary rehabilitation programmes (inpatients and day-hospital service) help address the full spectrum of patients' clinical needs. A key step in our pathway is the systematic reassessment of factors contributing to poor asthma control before confirming severe asthma or escalating to biologic therapy. Misdiagnosis and symptom misattribution are carefully considered, as patients with uncontrolled asthma may present alternative diagnoses or relevant comorbidities [1]. Inhaler technique is directly checked during clinical evaluation and reinforced through repeated educational interventions, if needed. When errors are observed, or when the device is poorly suited to the patient's characteristics, treatment delivery is optimized through retraining or device change. We consider incorrect inhaler technique, suboptimal adherence and inadequate self-management to be well-recognized but still major unmet needs in uncontrolled asthma; therefore, patient education, trigger avoidance and individualized self-management strategies are integrated into our multidisciplinary pathway.

Our outpatient clinic is tailored for uncontrolled asthma patients. Through priority medical appointments and dedicated agenda, flexibility and adaptability are granted, meeting the needs of unstable patients. In parallel, the MAC protocol has been designed to accelerate and speed-up the evaluation of most complex and severe cases. It is a structured day-hospital program that can last from 5 to 30 days, either consecutively or not. The MAC consists in a multi-day assessment and intervention that can facilitate comprehensive management and rapid phenotyping. Additionally, it provides opportunities for multiple consecutive educational interventions, incorporating key healthcare professionals such as psychologists, physiotherapists, and dietitians, who often require more time to deliver a complete educational intervention, alongside the standard team of respiratory specialists and nurses (Figure 2).

Phenotyping inflammation in severe asthma patients

Pheno-endotyping plays a central role in our centre, providing key information on patient characteristics, from inflammatory to functional aspects. This approach is essential for optimizing therapy and enabling tailored decision-making within the framework of precision medicine. Indeed, effective management of severe asthma requires addressing its clinical and biological heterogeneity, which reflects distinct underlying pathophysiological mechanisms. Comprehensive phenotypic assessment combining clinical features with inflammatory biomarkers facilitates accurate diagnosis, informs disease severity stratification, guides personalized treatment decisions, and enables monitoring of therapeutic response [20,21].

Indeed, a comprehensive evaluation of type 2 (T2) biomarkers, such as FeNO, blood eosinophils, sputum eosinophils, and IgE/atopy, is crucial to understand and characterise inflammatory phenotypes of patients with severe asthma, as it guides therapeutic decisions, especially the use of targeted biological therapies [1,22-24]. These core markers define the so called T2-high phenotype and enable clinician to identify patients eligible for biologics (anti-IL-5/IL-5R, anti-IL-4Rα, anti-IgE, or anti-TSLP) based on prescriptive/prognostic local criteria [1,22,25]. On the other hand, the definition of T2-low asthma still lacks consensus and reliable biomarkers for its identification, currently making it a diagnosis of exclusion based on the absence of T2-high biomarkers [26]. Currently, induced sputum analysis remains the only non-invasive method capable of directly assessing airway neutrophilia [26].

These biomarkers are variably accessible and have distinct advantages and limitations in clinical practice, but their integration is essential for optimal risk stratification and therapeutic decision-making in asthma. Although biomarker-based assessment and biologic therapies have substantially improved the management of severe asthma, important limitations remain in the implementation of precision medicine [20]. Inflammatory phenotypes may partially overlap and vary over time, particularly under the influence of corticosteroids, comorbidities, environmental exposures and targeted treatments. Moreover, validated biomarkers for T2-low asthma remain limited, and this phenotype is still largely defined by the absence of T2 high biomarker [20,26]. Predicting individual response to a specific biologic also remains challenging in real-world practice [27]; therefore, biomarker assessment should be interpreted within a multidimensional clinical framework and reassessed over time, particularly in cases of suboptimal response or treatment failure [1].

Sputum eosinophils and airway inflammation

In particular, our centre provides an evaluation of airway inflammation, a central feature of asthma pathophysiology, through induced sputum. This test represents the gold standard for non-invasive assessment of airway inflammation, as it allows the collection and cytological analysis of cells from the airways. The induction procedure and sample processing are conducted according to established international guidelines, followed by differential cell count analysis [28]. Although this technique can provide valuable information, it requires expertise and considerable time to perform. For this reason, it is difficult to implement in centers that are not highly specialized in the procedure, but when available can give additional information [29-31].

Asthma patients usually present an increased percentage of sputum eosinophils (≥3.0%) [32,33]. Four inflammatory patterns can be identified based on defined thresholds - although not always consistent between centres [26] - for eosinophil percentage (3%) and neutrophil percentage (61%), as shown in Figure 3 [32,33].

The presence of sputum eosinophils (central airway inflammatory biomarker) indicates a T2 inflammatory pattern, and the GINA report highlights its possible role in phenotyping and sputum-guided therapy [1]. Indeed, in adults with moderate-to-severe asthma and frequent exacerbations, adjusting treatment based on sputum eosinophilia has been shown to reduce exacerbation rates and glucocorticoid exposure without compromising asthma control or lung function. However, due to limited availability in routine clinical settings, this approach is currently recommended only in specialized centres with access to dedicated facilities [34-36].

In our centre, induced sputum is usually performed at baseline as part of comprehensive inflammatory phenotyping and repeated during follow-ups, generally at 6 months and annually thereafter. It may also be repeated according to clinical need, particularly in patients with persistent poor asthma control, frequent exacerbations, and suboptimal response to biologic therapy.

Multidisciplinary approach and specialists' roles

Extrapulmonary treatable traits are key contributors to asthma burden, significantly affecting outcomes and quality of life. The treatable traits approach supports personalized care by addressing the heterogeneity of asthma and its comorbidities. When left unmanaged, extrapulmonary traits can worsen current health and influence future disease progression. Targeted treatment of these traits has been shown to improve asthma control, reduce

exacerbations, and decrease overall disease burden [37]. To address the complexity of uncontrolled asthma, our clinic has built a multidisciplinary network, including allergologists, rheumatologists, radiologists, hematologists, and endocrinologists, to ensure timely, accurate evaluations and coordinated management. This team is continuously expanding, further enhancing our ability to deliver comprehensive care.

Allergen immunotherapy and asthma

Asthma is frequently associated with respiratory allergy, which predisposes susceptible individuals to asthma development through the "atopic march". This concept reflects a life-course trajectory of allergic diseases, from early sensitization to progressive airway involvement, occurring in parallel with the globally increasing prevalence of allergic disorders and asthma across all age groups.Allergen immunotherapy (AIT) is the only disease-modifying treatment targeting the underlying immunological mechanisms of IgE-mediated allergy, based on repeated administration of specific allergens to induce long-term tolerance and reduce clinical symptoms. For allergic asthma and allergic rhinitis/conjunctivitis, AIT, administered as subcutaneous (SCIT) or sublingual (SLIT) formulations, has proven to be a safe and effective targeted treatment in allergen-driven disease [38-40]. Its efficacy in asthma was first demonstrated in a double-blind placebo-controlled trial in 1954 [41], and it remains the only causal treatment for allergic diseases, with sustained benefits that may persist even after treatment discontinuation [42].

In patients with allergic asthma, particularly mild-to-moderate forms, AIT can be an effective adjunct to pharmacological therapy. The main indication is a clear association between symptoms and allergen exposure, confirmed by skin prick testing or specific IgE. AIT is generally considered when standard therapy fails to achieve adequate control, or when patients aim to reduce long-term medication use. Several studies and meta-analyses have shown that both SCIT and SLIT reduce asthma symptoms, medication requirements, and bronchial hyperresponsiveness, and may prevent progression from allergic rhinitis to asthma, as well as the development of new sensitizations [43,44].

However, AIT requires careful patient selection and is contraindicated in uncontrolled asthma because of the risk of systemic reactions, including anaphylaxis. Therefore, asthma control and lung function must be assessed before initiation. Although most patients with severe asthma exhibit an eosinophilic phenotype, many also display an allergic endotype, particularly in the presence of allergic rhinitis. Severe asthma patients are often poor candidates for AIT due to

frequent exacerbations. However, after achieving disease stability with biologic therapy, add-on AIT may become feasible. In this setting, AIT could potentially contribute to achieving clinical remission, possibly sustained even after biologic discontinuation [45]. Landmark trials combining AIT with biologics (omalizumab, dupilumab, or tezepelumab) have suggested synergistic effects, improving not only safety and tolerability, but also efficacy [45,46]. Tezepelumab has shown additive benefit with SCIT in allergic rhinitis, and preliminary data suggest similar effects in severe asthma, although further studies are needed to confirm these observations [47].

Overall, AIT represents a valuable therapeutic option in selected patients with allergic asthma and supports its integration into personalized treatment strategies, particularly in multimorbid allergic conditions [45].

Hypereosinophilia and eosinophil-associated diseases: focus on eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome

Eosinophil-associated diseases (EADs) comprise a broad group of conditions in which eosinophils contribute to tissue inflammation and organ damage. These range from common allergic respiratory disorders, such as asthma or chronic rhinosinusitis with nasal polyps (CRSwNPs), to rare systemic eosinophilic disorders, such as eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndromes (HES) [48]. In patients with persistent eosinophilia (500-1500 cells/μL) or hypereosinophilia (>1500 cells/μL on two separate occasions) in the setting of asthma and/or CRSwNPs, clinicians should consider an underlying systemic eosinophilic disease and initiate a comprehensive diagnostic workup [48-50].

EGPA is a rare systemic vasculitis affecting small- to medium-sized vessels, associated with anti-neutrophil cytoplasmic antibodies (ANCA) and characterized by eosinophil-rich granulomatous inflammation [48]. It typically presents in middle age, with a prevalence of approximately 15.6 cases per million and an annual incidence of 1.7 cases per million worldwide [51,52]. EGPA usually follows a triphasic course, progressing from late-onset asthma and/or CRSwNP, to eosinophilic tissue infiltration and, ultimately, vasculitic organ involvement [53,54]. Asthma, often glucocorticoid (GC)-dependent, is nearly universal in EGPA [55], while CRSwNPs affects up to 75% of patients [56]. Clinical presentation ranges from indolent eosinophilic inflammation to fulminant multiorgan vasculitis. ANCA positivity, directed against myeloperoxidase, occurs in about 30-40% of patients and contributes to phenotype stratification. ANCA-positive individuals more frequently display classic vasculitic

features (e.g. purpura, peripheral neuropathy, glomerulonephritis), whereas ANCA-negative disease is typically dominated by eosinophilic organ involvement, particularly affecting heart and lungs [57-59].

Diagnosis requires systematic evaluation of multisystemic involvement.Cutaneous manifestations, such as palpable purpura, ulcers, nodules, or urticarial lesions, are common and often require biopsy for histopathological confirmation [58]. Pulmonary involvement may extend beyond asthma including migratory infiltrates, eosinophilic pneumonia, or, less commonly, alveolar hemorrhage [60]. Peripheral neuropathy, often presenting as mononeuritis multiplex, affects up to 65% of patients and warrants neurophysiological assessment when suspected [61]. Cardiac involvement is a major prognostic determinant and ranges from subclinical abnormalities to overt myocarditis, cardiomyopathy or coronary vasculitis [62]. Cardiac biomarkers, echocardiography, and, in selected cases cardiac magnetic resonance imaging, are therefore essential for early detection and follow-up [63,64]. Renal involvement is less frequent than in other ANCA-associated vasculitis, but may range from isolated urinary abnormalities to rapidly progressive kidney injury [65]. Gastrointestinal manifestations vary widely, from mild symptoms to severe eosinophilic gastroenteritis or mesenteric vasculitis [66]. Lastly, EGPA is also associated with an increased risk of arterial and venous thromboembolic events, particularly around diagnosis [67], likely related to eosinophil-mediated prothrombotic mechanisms [68]. Among EADs, HES represents a challenging differential diagnosis, especially in ANCA-negative cases characterized by prominent eosinophilic manifestations without overt vasculitis. HES may include clonal, reactive, or idiopathic conditions [69]. Distinguishing idiopathic HES (iHES) from ANCA-negative EGPA is often difficult, as both are driven by T2 inflammation, with IL-5 as a key effector cytokine [70]. To address this overlap, revised classification frameworks have proposed the concept of “T2-HES”, characterized by asthma, CRSwNPs, and eosinophilic organ involvement without vasculitic features [71]. The dual-pathogenesis model of EGPA integrates a T2-driven eosinophilic inflammatory component with a neutrophil-mediated, ANCA-associated vasculitic process [57,72,73]. Recent reports have described EGPA onset in patients treated with anti-IL-5/IL-5R agents for severe asthma, with approximately two thirds of cases being ANCA-positive [74]. These observations raise the possibility that suppression of eosinophilic inflammation, particularly during GCs tapering, may unmask vasculitic mechanisms, although the underlying mechanisms remain unclear. Targeted biologic therapies have substantially reshaped the management of both EGPA and HES. Mepolizumab

has demonstrated efficacy in reducing relapse rates, GCs exposure, disease burden, and improving health-related quality of life (HRQoL) and is approved for the treatment of both conditions [75-77]. Benralizumab, an anti-IL-5 receptor α monoclonal antibody that induces near-complete eosinophil depletion, has shown clinical efficacy in both EGPA and HES [78-81], with recent approval for the treatment of EGPA.

The shared therapeutic response further supports the pathogenic overlap between these disorders and positions anti-IL-5 agents as central disease-modifying strategies, although their role in acute phases of vasculitis-dominant or ANCA-positive EGPA remains to be fully clarified. EGPA and iHES lie along a shared spectrum of T2-driven eosinophilic disorders. Understanding their intersections is essential for early diagnosis, accurate disease staging, and timely implementation of targeted therapies to optimize long-term outcomes.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory lung disease caused by immunologic reactions to *Aspergillus fumigatus* colonizing the airways of patients with asthma or cystic fibrosis [82]. Classic ABPA pathogenesis involves fungal sensitization to *Aspergillus* species, which promote eosinophilic proliferation and activation by enhancing the effects of IL-3, IL-5, and granulocyte colony-stimulating factor. The innate immune response to *A. fumigatus* in the lung leads to chemotaxis and activation of Th2 cells, which produce cytokines, including IL-4 and IL-5 that drive the differentiation of IgE-secreting plasmacytes and attract and activate eosinophils [83]. Eosinophils interact directly with *A. fumigatus* spores, generating eosinophilic extracellular traps that contribute to bronchial epithelial injury. Pulmonary eosinophilia represents the hallmark of ABPA. Clinical manifestations of ABPA include poorly controlled asthma, wheezing, hemoptysis, productive cough, and systemic symptoms, such as fever and weight loss. Characteristic central bronchiectasis and transient pulmonary opacities are commonly observed radiologic findings [84]. According to the revised 2024 ISHAM-ABPA working group criteria, the diagnosis of allergic bronchopulmonary aspergillosis (ABPA) should be considered in patients with predisposing conditions such as asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), or bronchiectasis, as well as in subjects presenting with a compatible clinico-radiological picture.

The diagnostic work-up is based on the presence of two essential components. First, patients must demonstrate sensitization to *A. fumigatus*, documented by *A. fumigatus*-specific IgE levels ≥0.35 kUA/L. Second, total serum IgE levels should be elevated, with a threshold ≥500 IU/mL.

In addition to these essential criteria, at least two of the following additional components are required for the diagnosis: positive IgG antibodies against *A. fumigatus*; peripheral blood eosinophilia ≥500 cells/µL (either current or historical); and radiological findings consistent with ABPA. Typical imaging abnormalities include central bronchiectasis, mucus plugging, high-attenuation mucus on chest CT, or transient/fleeting pulmonary opacities on chest radiography. Overall, the revised ISHAM 2024 criteria emphasize a comprehensive diagnostic approach integrating clinical predisposition, immunological evidence of *Aspergillus* sensitization, and characteristic radiological and laboratory findings [85].

Molecular allergens of *A. fumigatus* can improve the specificity of ABPA diagnosis by distinguishing genuine fungal sensitization from cross-reactivity. In particular, IgE against Asp f 1 and Asp f 2 confirms primary sensitization to *A. fumigatus*, whereas the additional detection of Asp f 4 IgE strongly supports the diagnosis of ABPA. Asp f 6 has also been associated with ABPA when combined with Asp f 1 and/or Asp f 2 positivity. Conversely, isolated sensitization to Asp f 3 may suggest sensitization to other fungal species rather than true *A. fumigatus* allergy. Therefore, molecular IgE profiling may complement conventional diagnostic criteria and support screening, diagnosis, and follow-up of ABPA [82].

The differential diagnosis of ABPA includes eosinophilic lung diseases such as EGPA, which shares features of asthma and rarely coexists with ABPA, suggesting common IL-5-driven mechanisms [86]. Other differential diagnoses include chronic eosinophilic pneumonia, HES, and cystic fibrosis. Imaging findings, total IgE levels, *Aspergillus*-specific serology, and ANCA testing aid in distinguishing these conditions. Standard treatment of ABPA relies on systemic GCs administered in a tapering regimen to control inflammation and immune activation. Antifungal agents, such as itraconazole or voriconazole, may be added to mitigate fungal burden and antigenic stimulation [82]. In patients with severe T2-high asthma, biologic therapies, including omalizumab, mepolizumab, benralizumab, dupilumab, or tezepelumab, may be considered as GC-sparing options, alongside bronchodilators and mucolytics [87,88]. Regular monitoring with imaging and serum IgE is essential to assess treatment response and prevent disease progression [85]. ABPA should therefore be actively investigated in the context of uncontrolled asthma, as early diagnosis and long-term management are crucial to prevent irreversible damage and fibrosis.

Upper airways comorbidities

Extrapulmonary treatable traits involving the ear, nose, and throat (ENT) are highly prevalent in patients with severe asthma and are associated with an increased risk of future exacerbations [89]. Upper airway diseases - including allergic rhinitis, chronic rhinosinusitis (CRS), and non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD), together with gastroesophageal reflux disease (GERD), represent some of the most frequently reported extrapulmonary traits in asthma registries. Vocal cord dysfunction (VCD), and obstructive sleep apnea further contribute to exacerbation risk. Targeting these extrapulmonary clinical domains through tailored therapeutic strategies can improve asthma control, reduce exacerbations, and ultimately decrease overall disease burden [90,91]. Effective implementation of this comprehensive management approach often requires close collaboration between pulmonologists and ENT specialists.

Allergic rhinitis and chronic rhinosinusitis

Allergic rhinitis is an inflammatory condition of the nasal mucosa triggered by allergen exposure and classified as seasonal or perennial. It frequently coexists with asthma, affecting approximately 60-80% of asthmatic patients, and is associated with poorer clinical control and increased exacerbation rates [90,92].

Optimal management of allergic rhinitis is therefore essential, not only for symptom relief but also for potential improvement in asthma outcomes. Therapeutic approaches include allergen avoidance, pharmacological therapies such as intranasal GCs and antihistamines, and immunotherapy in selected patients with more severe disease [90,93].

CRS, particularly CRSwNPs, as well as NERD, are common comorbidities in patients with uncontrolled or severe asthma, affecting up to 50-70% of this population. These conditions are characterized by persistent inflammation of the nasal and sinus mucosa and share key pathophysiological mechanisms with asthma, including T2-driven inflammation. CRSwNPs is associated with nasal polyp formation, whereas NERD is defined by hypersensitivity to NSAIDs and eosinophilic airway inflammation. Both conditions are linked to increased exacerbations and impaired HRQoL. Therapeutic management typically includes GC therapy, surgical interventions, and biologic agents, underscoring the importance of an integrated, multidisciplinary approach. Effective treatment of CRS and NERD has been shown to improve asthma outcomes, highlighting the relevance within comprehensive respiratory care strategies [90,92-95].

Vocal cord dysfunction

VCD is a respiratory condition characterized by paradoxical vocal fold motion during inspiration, resulting in transient upper airway obstruction. It affects approximately 4% of adults in general population, with a prevalence ranging from 10-20%, up to 40%, in patients with difficult-to-treat asthma. VCD shares triggers with asthma, including emotional stress, airway irritants, and physical exercise, and is often associated with comorbid conditions such as chronic rhinitis, GERD, and anxiety. Diagnosis can be challenging and is often delayed or missed, leading to inappropriate treatments and increased healthcare utilization. Laryngoscopy performed during symptomatic episodes remains the diagnostic gold standard, while the Pittsburgh VCD Index may support clinical suspicion. Management is primarily non-pharmacological, with laryngeal control therapy as the cornerstone, complemented by selected behavioral psychotherapy or pharmacological interventions when indicated [90,93]. Accurate diagnosis and targeted management can substantially improve patient outcomes and reduce unnecessary medical interventions.

Gastroesophageal reflux disease

GERD is a chronic condition affecting approximately 13.3% of the global population and is characterized by reflux of gastric contents leading to typical symptoms, such as heartburn and regurgitation, as well as extraesophageal symptoms that impair HRQoL. Established risk factors include older age, female sex, smoking, obesity, and NSAID use. GERD is highly prevalent among patients with asthma, with reported prevalence of 52.7% based on symptom assessment and 46.5% based on endoscopy and pH monitoring. Additionally, GERD is a key contributor to poor asthma control and frequent exacerbations. Two main mechanisms have been proposed: the reflux theory, involving micro-aspiration of gastric contents into the airways, and the reflex theory, which postulates vagally mediated bronchoconstriction. Diagnosis and management of GERD involve a multifaceted approach, incorporating symptom evaluation, empirical therapeutic trials, objective diagnostic testing, and a range of interventions from lifestyle modifications to pharmacological and, in selected cases, surgical treatments [93].

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a relevant comorbidity in difficult-to-treat and severe asthma, particularly in patients with obesity, rhinitis, nasal polyps and gastroesophageal reflux disease.

OSA may contribute to systemic and local inflammation, nocturnal symptoms, poor asthma control, impaired quality of life, and increased exacerbation risk [96]. In our centre, symptoms suggestive of sleep-disordered breathing are actively investigated, especially in patients with obesity and/or persistent nocturnal symptoms, and patients are referred for dedicated sleep assessment when clinically indicated. Although evidence on the impact of OSA treatment on asthma outcomes remains limited and heterogeneous, the identification and management of OSA should be considered an important component of a treatable traits approach [96].

Metabolic and endocrine comorbidities

Epidemiologic and experimental evidence support a complex and potentially bidirectional relationship between asthma and obesity. The risk of asthma seems to increase in overweight/obese individuals [97], and conversely obesity appears to be more common in asthma patients [98,99]. Obesity complicates asthma management by increasing hospitalization risk, reducing GCs responsiveness, and favoring disease relapse [100]. Cluster analyses have identified a distinct obesity-associated asthma phenotype, typically neutrophilic, with impaired lung function, more frequent exacerbation, and reduced GCs responsiveness [101-103]. This interaction is multifactorial and influenced by sex, age, genetics, diet, microbiome and vitamin D levels. Obesity induces immunologic changes, including adipose tissue infiltration by pro-inflammatory macrophages and disruption of classical Th2 pathways, leading to altered eosinophil trafficking and chronic low-grade airway inflammation. Non-atopic asthmatic subjects with obesity have higher sputum neutrophils, while those with the "atopy-obesity overlap" phenotype show increased sputum macrophage counts, suggesting that innate immune pathways are key in obesity-related asthma [103].

Elevated inflammatory cytokines may impair steroid signaling, contributing to GCs resistance [104]. Beyond obesity itself, high-fat diets worsen asthma outcomes through activation of innate immune pathways, including inflammasome signaling [105,106]. Obesity also affects lung mechanics by reducing lung volumes and increasing airway hyperreactivity, even in non-asthmatic individuals [107]. Metabolic syndrome, encompassing glucose and lipid abnormalities, hypertension, and elevated waist circumference, constitutes an additional risk factor for asthma onset, severity and exacerbation [108]. Related disorders of glucose metabolism may be further amplified by GCs exposure. Whether obesity precedes asthma onset or develops as a consequence of asthma-related treatments and reduced physical activity remains debated [109]. Regardless of temporal sequence, targeted weight-loss interventions -

including lifestyle, pharmacologic, or surgical strategies - are essential to improve asthma control, reinforcing the need for multidisciplinary management [105]. Regular monitoring of body weight and visceral adiposity should be incorporated into routine asthma care.

Glucocorticoid-related endocrine complications

GCs are central to asthma management, particularly for the treatment of exacerbations, and may also be required for several comorbidities frequently encountered in severe asthma clinics, such as CRSwNPs and EGPA; however, prolonged exposure, even at low systemic or local doses, is associated with increased risks of cardiovascular and metabolic disorders, infection, and osteoporotic fractures [110,111]. These adverse events are mediated by sustained supraphysiological steroid concentrations and collectively define exogenous (iatrogenic) Cushing's syndrome [110]. Risk varies according to steroid potency, pharmacokinetics, treatment duration, dosing schedule, and drug-drug interactions [111-113]. GC therapy exceeding two weeks evening dosing, or prolonged exposure to a daily dose above 4-6 mg of prednisone equivalent, suppresses the hypothalamic–pituitary–adrenal axis [113], a phenomenon that may also occur with inhaled or intranasal formulations. Abrupt discontinuation may result in adrenal insufficiency; therefore, gradual tapering and, when indicated, assessment of adrenal recovery with morning serum cortisol are recommended [113].

GC-induced bone loss develops rapidly and increases fracture risk. Current guidelines recommend early initiation of antiresorptive therapy in patients with prior fragility fractures or high fracture risk, regardless of age or GCs dose [114]. Although bone loss is partially reversible after GCs withdrawal, evidence of persistent fracture risk suggests that antiresorptive treatment duration should be individualized based on cumulative exposure and cumulative fracture risk [110]. Nonpharmacological strategies, including lifestyle modifications, adequate calcium and vitamin D intake, and use of the lowest effective steroid dose, remain essential prophylactic measures [110].

Clinicians should proactively identify and manage GC-related comorbidities and provide appropriate patient education [115].

Imaging abnormalities and differential diagnosis in severe asthma

Although imaging is not routinely required for asthma diagnosis, radiologists play a key role in the evaluation of difficult-to-treat asthma, as recognized by the Global Initiative for Asthma (GINA) [1].

Several imaging techniques may help clinicians to evaluate both morphologic and functional abnormalities in patients with asthma. Chest radiography is primarily used to assess acute complications, whereas HR-CT is essential for identifying alternative diagnoses and comorbid conditions. Accordingly, the American College of Radiology recommends CT imaging in complicated asthma to investigate conditions such as ABPA, eosinophilic pneumonia, or systemic vasculitis [116].

HRCT may reveal bronchial wall thickening, bronchiectasis, mucus plugging, air trapping, atelectasis, or interstitial abnormalities, improving phenotype characterization and interpretation of clinical findings [117]. The prevalence and extent of these abnormalities increase with asthma severity and disease duration [118-123].

Bronchial wall thickening is the most frequent HRCT finding, seen in over half of severe asthma patients, and correlates with airflow limitation and reduced FEV_1, while bronchiectasis is more common in patients with long-standing disease and impaired lung function. Mucus plugging is particularly associated with severe eosinophilic asthma and has been linked to ventilation defects. Quantitative scoring systems for mucus plugs may support disease phenotyping and monitoring of therapeutic response to biologics [118,119,121,124-127].

Air trapping, best visualized on expiratory CT, correlates with indices of small airway dysfunction and irreversible airflow limitation [128-131]. Less frequent findings include emphysema, atelectasis, ground-glass opacities, and consolidation [122,130]. When present, ground-glass opacities and consolidation may indicate eosinophilic infiltrates or organizing pneumonia and warrant prompt exclusion of systemic eosinophilic or vasculitic disorders, including EGPA [116,132].

Pulmonary rehabilitation

Our centre is equipped to provide a structured rehabilitation intervention for both inpatients and out-patients (day-hospital) settings. Pulmonary rehabilitation (PR) is an evidence-based, multidisciplinary, and integrative intervention to enhance both the physical and psychological well-being of individuals with chronic respiratory diseases while fostering sustained adherence to health-promoting behaviours; it involves a comprehensive patient assessment, followed by

individualized therapeutic strategies, including but not limited to exercise training, patient education, and behavioural modifications [133]. Randomized controlled trials have documented its positive impact on exercise capacity, symptom management, and health-related quality of life in patients with several respiratory disease, including asthma [134]. Its impact on asthma seems to be less pronounced than in patients with chronic obstructive pulmonary disease (COPD), and the evidence is uncertain and not always consistent [135-139]. However, previous studies have suggested its potential efficacy in the sub-group of severe asthmatic patients. Indeed, some authors reported improvements in asthma control and/or symptoms [140-145], as well as exercise capacity [143,144]. Additionally, preliminary data suggested a possible role in reducing asthma exacerbations [140,142] and glucocorticoid usage [140]. Moreover, home-based PR also seems to have a beneficial impact on severe asthma, as it has been associated with an improved exercise tolerance and quality of life [146].

Future perspective and conclusions

Our tertiary asthma clinic highlights how precision medicine and treatable traits approach can be effectively implemented in real-world practice. By offering a structured, patient-centred service, including prioritized outpatient access, comprehensive day-hospital program (MAC), advanced phenotyping/endotyping, multidisciplinary team assessment and PR, we ensure timely and personalised care for uncontrolled or severe asthma patients. This multidisciplinary, educational, and diagnostic pathway allows a systematic identification and treatment of modifiable traits, supports the most appropriate therapeutic decisions, and may lead to improved outcomes and more efficient disease management in line with the principles of modern asthma care.

In the near future, expanding our severe asthma clinic toward a “united airways disease” clinic may offer additional benefits for our patients, recognising that chronic inflammatory diseases of the upper and lower airways - such as asthma, chronic rhinosinusitis, and COPD - may coexist and share common pathophysiological mechanisms, including type 2 inflammation. Integrating care for these conditions may enable a better approach to complex airways diseases, particularly in light of the new data regarding biologic agents targeting selected COPD phenotypes [147].

Moreover, multidisciplinary integration is expected to play an increasingly important role not only in severe asthma, but also in overlapping inflammatory airway and systemic diseases sharing common pathogenic pathways and therapeutic targets. In this context, coordinated

specialist assessment may improve the identification of treatable traits, support appropriate biologic treatment selection, and promote integrated management of patients with complex inflammatory phenotypes. In the end, our primary goal is to provide the best possible care for our patients by continuously evolving our clinic through the integration of active research and clinical practice, and by progressively implementing the latest concepts in asthma and airway disease management as they emerge.

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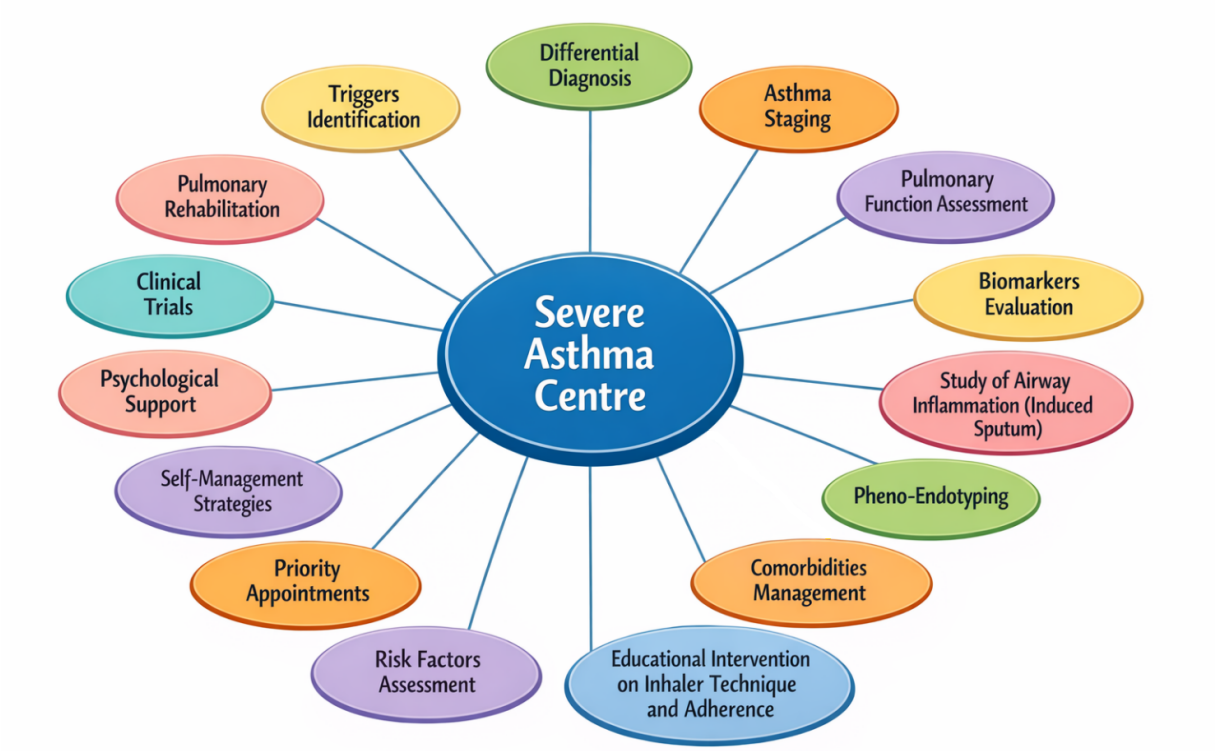

Figure 1. Severe asthma center integrated approach and assessments. Figure generated using OpenAI's ChatGPT image generation tool.

Figure 2. Health-care specialists involved in our center. Figure generated using OpenAI's ChatGPT image generation tool.

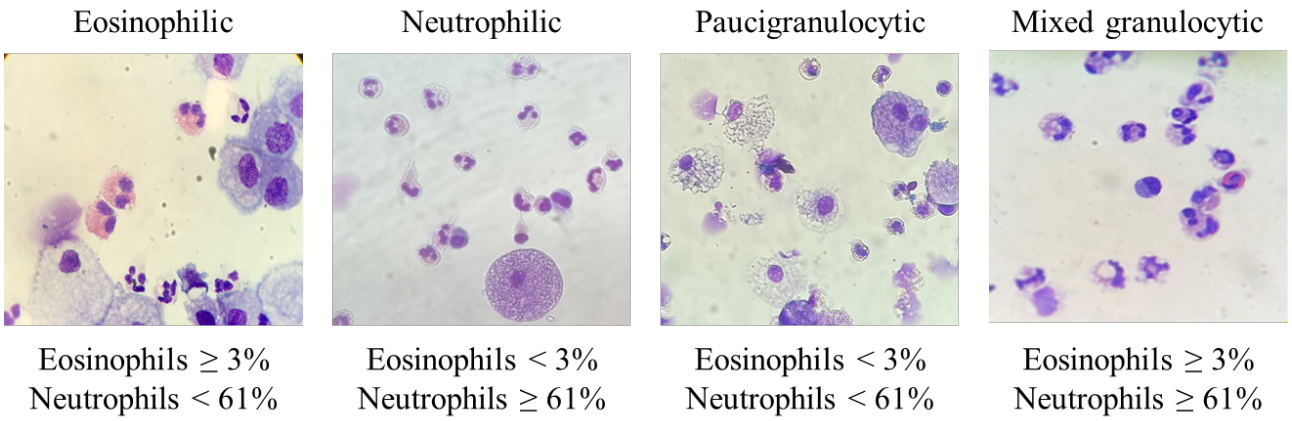

Figure 3. Different airway inflammatory patterns evaluated with induced sputum.