Severe asthma, COPD: Why symptom control isn't enough

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For clinicians managing chronic respiratory diseases, the distinction between stable disease and impending crisis can be subtle. Severe asthma and chronic obstructive pulmonary disease (COPD) represent a significant burden, not just in terms of daily symptoms, but in the life-altering impact of acute exacerbations. These events drive hospitalisations, accelerate disease progression, and ultimately diminish quality of life for millions across Europe.

The challenge lies in identifying the moment when standard maintenance therapy is no longer sufficient and more aggressive, targeted interventions are warranted. This requires a clear understanding of disease mechanisms and the available therapeutic arsenal, moving beyond reactive management to proactive disease modification. The Oxford Handbook of Respiratory Medicine provides a concise reference for navigating these complex decisions.

KEY TAKEAWAYS

- The Pivot: Recognising severe asthma and COPD requires a shift from symptom control to preventing future exacerbations and preserving lung function.
- The Data: Early identification of inflammatory phenotypes, particularly eosinophilic inflammation, guides the selection of targeted biologic therapies.
- The Action: Clinicians should rigorously assess patients for severe disease criteria and consider advanced therapies when conventional treatments fail to achieve control.

Severe asthma, by definition, is asthma that remains uncontrolled despite high-dose inhaled corticosteroids (ICS) and a second controller, or requires systemic corticosteroids to maintain control. It affects a significant minority of asthma patients, estimated at 5-10% of the total asthma population, but accounts for a disproportionate share of healthcare costs and morbidity. These patients often experience frequent exacerbations, hospitalisations, and a progressive decline in lung function, despite adherence to guideline-recommended therapies. The underlying pathophysiology is complex and heterogeneous, involving various inflammatory pathways beyond the typical Th2-driven eosinophilic inflammation seen in milder forms of the disease. This heterogeneity complicates treatment decisions, necessitating a more precise approach to patient stratification.

COPD, on the other hand, is a progressive lung disease characterised by persistent respiratory symptoms and airflow limitation that is due to significant exposure to noxious particles or gases, most commonly cigarette smoke. While smoking cessation and bronchodilators remain the cornerstones of management, a subset of patients with severe COPD

also experiences frequent exacerbations, often driven by inflammatory processes that overlap with those seen in asthma. These exacerbations are critical events, leading to accelerated lung function decline, reduced physical activity, and increased mortality. Identifying patients at high risk of exacerbations is paramount for effective management, as is understanding the specific inflammatory drivers in each individual.

Defining the Unmet Need

The unmet need in both severe asthma and COPD is substantial. Despite the availability of numerous inhaled therapies, a significant proportion of patients continue to suffer from persistent symptoms, impaired quality of life, and recurrent exacerbations. For severe asthma, the challenge lies in overcoming corticosteroid resistance and targeting specific inflammatory pathways that are not adequately addressed by conventional treatments. Patients often face a cycle of exacerbations, oral corticosteroid (OCS) dependence, and associated systemic side effects, including osteoporosis, diabetes, and cataracts. This reliance on OCS is a major driver of long-term morbidity and mortality, underscoring the need for OCS-sparing strategies.

In severe COPD, the focus shifts to preventing exacerbations and slowing disease progression. While bronchodilators improve symptoms and exercise tolerance, they do not fully address the inflammatory component that drives exacerbations in many patients. The presence of eosinophilic inflammation, even in COPD, has emerged as a key biomarker for identifying patients who may benefit from targeted anti-inflammatory therapies. But accurately identifying these patients and integrating advanced therapies into routine clinical practice remains a hurdle. The heterogeneity of COPD phenotypes means that a one-size-fits-all approach is often ineffective, demanding a more personalised treatment strategy.

Current Therapeutic Landscape and Guidelines

Current guidelines for severe asthma recommend a stepwise approach, escalating therapy based on symptom control and exacerbation frequency. This typically begins with high-dose ICS combined with a long-acting beta-agonist (LABA). If control remains elusive, a long-acting muscarinic antagonist (LAMA) may be added. For patients with persistent symptoms or exacerbations, particularly those with evidence of type 2 inflammation (e.g., elevated blood eosinophils, high fractional exhaled nitric oxide [FeNO]), biologic therapies targeting specific cytokines or receptors are indicated. These include monoclonal antibodies against IgE (omalizumab), IL-5 (mepolizumab, reslizumab, benralizumab), or IL-4Rα (dupilumab). Each biologic targets a distinct pathway, making patient selection based on inflammatory phenotype critical for optimising outcomes. For example, dupilumab has shown superiority over omalizumab in specific high-biomarker asthma populations.

For COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report provides comprehensive recommendations for diagnosis, management, and prevention. Initial management focuses on smoking cessation, vaccinations, and bronchodilator therapy (LABA and/or LAMA). For patients with frequent exacerbations, particularly those with elevated blood eosinophil counts, ICS may be added to LABA/LAMA combinations. The role of biologics in COPD is still evolving, but emerging evidence suggests that some anti-eosinophilic therapies, similar to those used in asthma, may reduce exacerbations in a subset of COPD patients with a strong eosinophilic phenotype. This overlap in inflammatory mechanisms highlights the potential for shared therapeutic strategies, as discussed in our previous coverage on epithelial cytokines linking severe asthma, CRSwNP, and COPD.

The Role of Biomarkers in Guiding Therapy

Biomarkers play a key role in identifying patients most likely to respond to targeted therapies. In severe asthma, blood eosinophil count is the most widely used and validated biomarker for predicting response to anti-IL-5 and anti-IL-4R± biologics. Higher eosinophil counts generally correlate with a greater likelihood of response, particularly in reducing exacerbation rates and OCS use. FeNO is another important biomarker, reflecting airway inflammation and predicting response to ICS and, in some cases, biologics. These biomarkers help clinicians move beyond a trial-and-error approach, enabling a more personalised and effective treatment strategy. The utility of these markers is not absolute, however, and clinical judgment remains essential, especially when considering the full patient profile.

In COPD, the utility of biomarkers is less established but gaining traction. Blood eosinophil count has emerged as a key predictor of response to ICS in patients with frequent exacerbations. Patients with higher eosinophil counts (e.g., >300 cells/µL) are more likely to benefit from ICS, while those with lower counts may experience increased risks of pneumonia without significant exacerbation reduction. This has led to a more precise approach to ICS use in COPD, reserving it for those most likely to benefit. Other biomarkers, such as periostin or IgE levels, are under investigation for their potential to identify specific COPD phenotypes that might respond to novel therapies, but they are not yet routinely used in clinical practice. The challenge lies in standardising these measurements and integrating them into routine clinical workflows, which is often easier said than done in a busy general practice setting. For a comprehensive overview of clinical examination and diagnostic tools, the 3M Littmann Classic III Stethoscope remains an indispensable tool.

When to Escalate: The Clinical Imperative

The decision to escalate therapy in severe asthma and COPD is driven by persistent symptoms, frequent exacerbations, and evidence of disease progression despite optimal conventional management. For severe asthma, this typically means patients who continue to experience two or more exacerbations per year requiring OCS, or who require continuous OCS to maintain control, despite high-dose ICS/LABA. These patients are at high risk of irreversible airway remodelling and long-term systemic complications from OCS. Early referral to a specialist centre for phenotype assessment and consideration of biologic therapy is essential for preventing worse long-term outcomes. Delaying these interventions can lead to worse long-term outcomes and a greater burden on healthcare systems. Our previous article on severe asthma: beyond airway focus in treatment decisions further explores this.

In COPD, escalation is indicated for patients with frequent exacerbations (e.g., two or more moderate exacerbations or one hospitalisation per year) despite optimal bronchodilator therapy. The presence of a significant eosinophilic component (e.g., blood eosinophils >100-300 cells/µL) should prompt consideration of adding ICS. For those who continue to exacerbate despite triple therapy (ICS/LABA/LAMA), or who have specific inflammatory phenotypes, further specialist evaluation is warranted. This might involve considering novel anti-inflammatory agents or exploring non-pharmacological interventions such as pulmonary rehabilitation. The goal is to break the cycle of exacerbations, which are not merely inconvenient but are critical events that accelerate disease progression and increase mortality. The ongoing research into AAT protein's role in lung health also points to new avenues for understanding and treating these complex conditions.

The Catch: Challenges in Implementation

Despite the clear benefits of targeted therapies, several challenges impede their widespread and timely implementation. One significant hurdle is the accurate identification of severe disease and appropriate inflammatory phenotypes in routine clinical practice. This requires access to diagnostic tools, such as blood eosinophil counts and FeNO measurements, and a clear understanding of their interpretation. But many primary care settings lack the resources or expertise for comprehensive phenotyping, leading to delays in referral and treatment initiation. The cost of biologic therapies also presents a barrier, often requiring stringent approval criteria and specialist oversight, which can further delay access for eligible patients.

Patient adherence to complex treatment regimens, particularly inhaled therapies, remains a persistent problem. Even with the most effective drugs, poor adherence can negate potential benefits, leading to perceived treatment failure and unnecessary escalation. Education and shared decision-making are critical to improving adherence and ensuring patients understand the importance of their therapy. The transition from oral corticosteroids to biologic-sparing regimens also requires careful management, as patients may experience withdrawal symptoms or a temporary worsening of symptoms during the tapering process. This necessitates close monitoring and support from a multidisciplinary team. The question of why benralizumab patients still suffer asthma attacks highlights the ongoing need for better understanding and patient selection.

The long-term safety and efficacy of newer biologics, particularly in real-world settings and diverse patient populations, continue to be evaluated. While clinical trials provide robust evidence, real-world data often reveal aspects not captured in controlled environments. This ongoing surveillance is essential for refining treatment guidelines and ensuring that these powerful therapies are used appropriately and safely. The emergence of real-world cohort data for dupilumab in severe asthma is a welcome development in this regard.

The next generation of therapies will likely focus on even more precise targeting of inflammatory pathways and addressing non-type 2 inflammation in severe asthma, as well as exploring novel anti-inflammatory and anti-fibrotic agents for COPD. The goal is to move beyond broad-spectrum immunosuppression towards highly specific interventions that minimise side effects and maximise efficacy for individual patients. This will require continued research into disease mechanisms, the development of new biomarkers, and innovative trial designs to evaluate these therapies effectively. The future of managing severe respiratory diseases lies in precision medicine, where treatment decisions are guided by a deep understanding of each patient's unique pathophysiology.

CLINICAL IMPLICATIONS

The persistent reliance on oral corticosteroids for severe asthma and COPD patients is a clinical failure. These agents carry a heavy burden of systemic side effects, often outweighing their short-term benefits in the long run. Clinicians must be proactive in identifying patients who meet criteria for severe disease and are candidates for biologic therapies, rather than waiting for multiple exacerbations to accumulate.

The availability of targeted biologics represents a significant advance, but their optimal use hinges on accurate patient phenotyping. Blood eosinophil counts and FeNO are not merely academic markers; they are practical tools that should guide prescribing decisions. Delaying referral to specialist centres for comprehensive assessment only prolongs patient suffering and increases the risk of irreversible lung damage.

For the pharmaceutical industry, the focus must shift beyond simply demonstrating efficacy in clinical trials.

> Real-world data on long-term outcomes, cost-effectiveness, and impact on OCS reduction are essential for broader adoption. Developing accessible diagnostic tools and educating primary care clinicians on their interpretation will be key to unlocking the full potential of these advanced therapies.
> The goal is to extinguish the embers of chronic inflammation before they ignite into full-blown exacerbations. This requires a collaborative approach between primary care, specialists, and industry, ensuring that patients receive the right treatment at the right time to preserve lung function and improve their quality of life.

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