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# Towards precision medicine in severe asthma: treatment algorithms based on treatable traits

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**Abstract**

Asthma is a common disease, and although its clinical manifestations may be similar among patients, recent research discoveries have shown that it consists of several distinct clinical clusters or phenotypes, each with different underlying molecular pathways yielding different treatment responses. Based on these observations, an alternative approach - known as 'precision medicine' - has been proposed for the management of patients with severe asthma. Precision medicine advocates identification of treatable traits, linking them to therapeutic approaches targeting genetic, immunological, environmental, and/or lifestyle factors in individual patients. The main "goal" of this personalized approach is to enable choosing a treatment which will be more likely to produce a beneficial response in the individual patient rather than a 'one size fits all' approach. The aim of the present review is to discuss different ways of phenotyping asthma and to provide a rationale for treatment algorithms based on principles of precision medicine.

**Keywords:**

asthma

precision medicine

biologics

phenotype

endotype

biomarkers

**Introduction**

Asthma is a common disease, characterized by chronic airway inflammation and hyperresponsiveness to various triggers, presenting with symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity together with variable expiratory flow limitation [1]. According to guidelines, asthma is characterized as severe, when adequate control cannot be achieved by high-dose treatment with inhaled corticosteroids and additional controllers or by oral corticosteroid treatment or is lost when the treatment is reduced [2]. Although clinical manifestations may be similar among patients, severe asthma is a heterogeneous and complex disease with variable response to standard treatment. Recent research has shown that several genes contribute to the development of asthma and the underlying immunological pathways [3]. Despite increasing prevalence worldwide, [4], in recent years morbidity and mortality of asthma have decreased, probably as a result of improvements in asthma management including targeted therapeutic options [5].

Severe asthma consists of several distinct clinical clusters or phenotypes, consisting of several inflammatory phenotypes each with different underlying molecular pathways (endotypes) yielding different treatment responses [3, 6]. The "traditional" distinction of asthma endotypes is mainly based on the discrimination of Th-2 high and Th-2 low inflammatory responses [7], however, the discovery of innate lymphoid cells (ILCs) and the fact that they are also capable of releasing Th-2 cytokines, results in a better discrimination of asthma into type-2 and non-type-2, with the former to be currently the best defined endotype [8]. Furthermore, endotyping asthma as Th-2 high and Th-2 low has several limitations: First, this

concept cannot explain the observation that airway hyper-responsiveness and airway remodeling are not directly linked to inflammation [9]. Second, it does not provide answers on why traditional T-cell immunosuppressives often do not work in asthma [10]. Furthermore, it does not answer the question why several patients suffer from severe asthma or have recurrent exacerbations despite optimal treatment [3, 11] and, finally, it excludes other interventions which are not based on a pharmacological approach.

As a heterogeneous disease, severe asthma can present with many – partly overlapping - clinical phenotypes, defined on the basis of measurable characteristics including age of onset, degree of airway obstruction and comorbidities. Based on these observations, a novel approach (known as 'precision medicine') has been proposed for the management of patients with chronic inflammatory airway diseases, based on treatable traits replacing disease labels such as 'asthma' or 'COPD'. Precision medicine advocates identification of treatable traits, linking them to therapeutic approaches targeting genetic, immunological, environmental, and/or lifestyle factors in individual patients [12]. The main "goal" of this personalized approach is to enable choosing a treatment which will be more likely to produce a beneficial response in the individual patient rather than a 'one size fits all' approach [13].

The aim of the present review is to discuss different ways of phenotyping asthma and to provide a rationale for treatment algorithms based on principles of precision medicine.

**Inflammatory phenotypes**

One of the most common ways to phenotype asthma is to determine the inflammatory profile in endobronchial biopsies [14] or less invasively, by induced sputum analysis [15]. Based on inflammatory cell differentials in induced sputum, asthmatic patients can be classified into four different inflammatory phenotypes i.e eosinophilic, neutrophilic, mixed and paucigranulocytic phenotype [15]. Each of these phenotypes is characterized by different inflammatory pathways, responds differently to therapeutic interventions and has been successfully used in order to optimize asthma treatment [16-18].

***Eosinophilic phenotype***

The eosinophilic phenotype is generally characterized by ≥2-3% sputum eosinophils although there are no universally accepted thresholds [15]. The eosinophilic inflammatory phenotype accounts for approximately 40-60% of the total asthma population [19, 20] and is usually associated with T2 inflammation with an increased release of T2 cytokines such as interleukin (IL)-4, IL-5 and IL-13. Since sputum induction requires an experienced staff and dedicated laboratory technicians, alternative non-invasive methods have been proposed. These methods include the measurement of fraction of exhaled nitric oxide (FeNO) (with a suggested cut off value of ≥42ppd) [21, 22] and absolute blood eosinophil count (with a suggested cut off value of ≥400/μL) which are both able to detect a sputum eosinophil count of ≥3% with acceptable accuracy [19, 23]. Traditionally, T2 cytokines were known to be produced by T helper (Th-2) lymphocytes and associated with allergic sensitization [24]. However, more recently, studies have shown that these cytokines can also be produced by innate lymphoid cells (ILCs), also resulting in tissue eosinophilia [25].

Patients with eosinophilic asthma are known to respond to standard treatment with inhaled corticosteroids (ICS) [1], and guiding therapy according to sputum eosinophils resulted in superior asthma control compared to traditional clinical outcomes [18, 26]. In some cases, airway eosinophilia persists despite treatment with high doses of ICS or even oral corticosteroids (OCS). In these cases, patients should be first evaluated for noncompliance, inadequate inhaler technique, ongoing allergen exposure, and comorbidities (i.e. rhinitis and conjunctivitis in allergic asthma and chronic rhinosinusitis, nasal polyps, vocal cord dysfunction, gastroesophageal reflux disease for late onset eosinophilic asthma) [19]. Patients with corticosteroid-resistant eosinophilic airway inflammation qualify for targeted (biologic) therapies which have been shown to improve asthma control and act as steroid sparing agents [27-30]. Anti-IgE monoclonal antibody (omalizumab) was the first approved biologic treatment for patients with severe allergic asthma uncontrolled with standard therapy [31]. In non-allergic patients with uncontrolled eosinophilic asthma despite treatment with high doses of ICS plus LABA combinations with or without OCS, anti-IL-5 therapies should be considered [1, 19]. Based on differences in mechanism of action, mepolizumab works best in patients on high doses of ICS with or without low doses of OCS [29], while reslizumab [32] and benralizumab [33] may be preferred in patients with persistent eosinophilia despite high doses of OCS. It should be mentioned that anti-IL-5 therapies have been administered to asthmatic patients with eosinophilia defined by blood eosinophils at different cut-off values ranging from 150 to 400 cells/mcL [29, 32, 33]. It is also very important to keep in mind that in patients with persistent eosinophilia, systemic disease such as Eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndromes which

also present with asthma and eosinophilia should be excluded before been considered for biological therapies. Patients with either eosinophilic or non-eosinophilic asthma with high FeNO levels might be improved with anti-IL-4/IL-13 therapies such as dupilumab [30, 34] although more recent evidence points towards a superior response in those with increased baseline blood eosinophil levels [35]. The key question in asthmatics with persistent eosinophilia is to determine which targeted approach is more effective due to heterogeneity in underlying mechanisms and since substantial overlap exists in daily clinical practice. Finally, in some cases like obesity associated asthma the absence of eosinophilic biomarkers either in sputum and/or in exhaled breath cannot always exclude the presence of eosinophilia in bronchial tissue [36].

***Neutrophilic phenotype***

The neutrophilic phenotype is characterized by a neutrophilic proportion ≥61% in induced sputum [15, 18, 37] although different cut off values have been used by different researchers ranging from 40-76% [6, 20, 38]. It is uncertain which cut off value corresponds with activated neutrophils contributing to the pathogenic process, since blood neutrophils do not correlate to airway neutrophils [20], and sputum neutrophil count does not correlate with bronchial tissue numbers or other markers of airway inflammation thus questioning their actual contribution to the airway pathology [39].

The neutrophilic phenotype accounts for 5-22% of patients [19, 40, 41] often related to more severe disease with compromised pulmonary function and worse asthma control [6, 42]. Patients with neutrophilic asthma do not respond or poorly respond to ICS [16], however it is unclear if this corticosteroid insensitivity is related

to the presence of neutrophils per se or if this is determined by the mechanisms underlying neutrophil recruitment [43].

There is evidence that neutrophilic asthma is linked to neutrophilic activation reflected by increased levels of IL-8 and IL-1β in induced sputum [44]. Innate immunity also seems to play an important role in neutrophilic airway inflammation in asthma via the expression of Toll Like receptors (TLR)- 2 and 4 and CD14 in sputum cells [44]. One possible pathway leading to neutrophilic inflammation is the induction of several chemoattractants such as IL-8, LTB4, MMP-9 and CXCL-1 by various stimuli in the airway epithelium (e.g. infections, pollutants or allergens) [45]. IL-17A and IL-17F are produced by Th17 cells and stimulate the production of IL-8 and CXCL1 from the airway epithelium which also are neutrophil chemoattractants [46], while Th1 cells are also associated with neutrophilic inflammation by producing INF-γ and TNF-α. Neutrophilic inflammation caused by the aforementioned pathways, results in airway damage and remodeling, mucus gland hyperplasia and hypersecretion and corticosteroid insensitivity [45]. It has been reported that severe neutrophilic asthma is related to higher levels of Th17 cytokines such as CXCL1, CXCL10, CCl-2, IL-6 and IL-8 compared to other inflammatory endotypes [47].

Neutrophilic asthma is common in smokers with asthma [48], in obese asthmatics [49] and occupational asthma [50, 51]. First of all, it is known that corticosteroid treatment reduces the apoptosis of neutrophils and contributes to Th-17 mediated neutrophilic inflammation [52]. Furthermore, the apoptosis of neutrophils might also be reduced by the release of mediators from bronchial epithelial cells as described above and phagocytosis of airway neutrophils from macrophages is also impaired [53]. Finally, airway neutrophilia can also be associated

with chronic airway infections (e.g.in bronchiectasis) or with an altered airway microbiome [53, 54].

Although blood eosinophils seem to be a good predictor of sputum eosinophilia, this is not the case in neutrophilic asthma in which blood neutrophilia cannot predict airway neutrophilia [20]. In clinical practice, besides sputum cell count, there are no other specific biomarkers for the discrimination of neutrophilic asthma. Increased levels of IL-8, which is known to activate neutrophils, have been found in patients with neutrophilic asthma [40] and correlated to sputum neutrophil count [55]. Other important biomarkers of neutrophil activation in patients with neutrophilic asthma are myeloperoxidase (MPO) and neutrophil elastase and can be detected in induced sputum samples [56, 57]. TNF-α [58] and IL-17 [59] are also related to neutrophilic inflammation in asthma.

To date, there are no targeted therapeutic interventions for patients with neutrophilic asthma. Presently, macrolides are often applied in refractory neutrophilic asthma, although these antibiotics may induce an increased risk of adverse events and increase bacterial resistance [60]. The anti-inflammatory activity of macrolides includes inhibition of transcription factors such as NFκB, reduction of activation and migration of neutrophils [61], restoration of corticosteroid insensitivity through inhibition of phosphoinositide 3 kinase (PI3K) and increase in histone deacetylase (HDAC)2 activity [62]. Although in one study which included smoking asthmatics the use of azithromycin did not show any improvement of asthma control or lung function [63], azithromycin significantly improved asthma exacerbations and quality of life in both eosinophilic and non-eosinophilic asthma [64]. Similarly, the use of clarithromycin in patients with neutrophilic asthma

resulted in reduction of neutrophilic inflammation accompanied by improvements in asthma control [65]. Statins have been used in clinical trials, however despite alterations in several inflammatory markers their use was not associated with improvements in asthma control or lung function parameters [45]. Cysteine X cysteine chemokine receptor 2 (CXCR2) has been recently used in asthmatic patients with neutrophilic airway inflammation with subsequent reduction in sputum neutrophils and exacerbation rate and a trend towards improvement in asthma control [66]. Finally, brodalumab, an anti-IL-17RA monoclonal antibody, and anti-TNF-α agents have been tested in asthma but failed to show substantial clinical effectiveness, while anti-TNF-α treatment was associated with serious infections [45]. In asthmatic smokers with neutrophilic asthma smoking cessation resulted in reduction of neutrophilic inflammation and lung function improvement [67].

***Paucigranulocytic phenotype***

Asthmatic patients with both neutrophil levels <61% and eosinophil levels <2% are classified as having paucigranulocytic asthma [15]. The frequency of this phenotype in asthmatic patients ranges from 17%-48% in different studies [20, 40, 41]. Although very little is known about the paucigranulocytic phenotype, in the majority of patients with paucigranulocytic asthma the absence of inflammatory cells is usually related to adequate asthma control and thus, it has been suggested that paucigranulocytic asthma may represent previous eosinophilic inflammation that has been successfully treated with corticosteroids [40]. However, some patients suffer from severe refractory asthma (SRA) and have poor asthma control despite absence of inflammatory cells in sputum [40] which may be related to intrinsic alterations in

structural cell function (such as epithelial, smooth muscle cells, vessels and nerves) [68].

There is evidence that airway epithelial cells, smooth muscle cells and nerves can orchestrate airway inflammation [68, 69] by secreting a variety of factors, including cytokines, chemokines and eicosanoids with autocrine or paracrine action which modulate basic cellular functions in a way that seems not to be inhibited by corticosteroids [70]. This is probably (one of) the reason(s) why patients with paucigranulocytic asthma present corticosteroid insensitivity.

Currently, there are no specific therapeutic approaches for patients with paucigranulocytic asthma. Although apart from bronchodilators, bronchial thermoplasty (BT) might be a possible therapeutic intervention, long term effectiveness or adverse events have not been fully evaluated in paucigranulocytic asthma and this intervention should be evaluated in the context of a clinical study [1]. BT delivers targeted thermal energy to the airway wall ablating airway smooth muscle (ASM) cells with subsequent decrease in the ASM mass [71] while it has been shown that it also modulates mucosal inflammatory responses and collagen deposition [72, 73]. This intervention has been shown to reduce asthma exacerbations and to improve lung function and health related quality of life [74-76]. Furthermore, it can be speculated that macrolides may be an effective in paucigranulocytic asthma since in a recently published study beneficial effects of azithromycin were observed irrespective of the underlying airway inflammation [64].

***Mixed inflammatory phenotype***

When both neutrophils and eosinophils are increased, patients can be classified as having mixed granulocytic asthma [15]. In order to categorize a patient in the mixed inflammatory phenotype, there has to be evidence of both increased count of neutrophils and eosinophils in induced sputum, independently or concurrently, on at least two occasions [77]. Studies have shown that asthmatics with a mixed inflammatory phenotype have more severe airflow obstruction, more frequent exacerbations and daily symptoms, and increased health care utilization compared to with pure eosinophilic or neutrophilic phenotypes [78]. Patients with mixed inflammatory phenotype express biomarkers related to both eosinophils and neutrophils. Higher concentrations of IL-6, a pleiotropic cytokine that can be produced by many cell types in response to a wide array of inflammatory stimuli, have been found in patients with the mixed inflammatory phenotype [79]. According to the above, although currently there are no combined targeted treatment options for patients with mixed inflammatory phenotype, preliminary evidence suggests that therapies targeting the IL-6 pathway may be beneficial [79].

**Stability of inflammatory phenotypes**

There is concern regarding the long-term stability of the aforementioned inflamamatory asthma phenotypes and data are conflicting. Prospective studies have shown that airway eosinophilia can persist for at least 5 years in a large proportion of asthmatic patients ranging from 54-88% [80, 81] and this has been confirmed in large cohort studies such as the Pan-European BIOAIR cohort [82] and the British Thoracic Society (BTS) Severe Asthma Registry [83]. Sputum cell counts may alter with therapy: e.g. eosinophilia can develop following reduction in the dose of corticosteroids [84]. Additionally, air pollution and airway infections can induce

airway neutrophilic inflammation [85], while airway neutrophilia can also be a considered as a consequence of corticosteroid use [43]. Finally, numerous other factors such as ageing [86], dietary [87] and smoking habits [88] as well as alterations in the airway microbiome [54] are also recognized to increase the number or airway neutrophils resulting in the observation that stability of the neutrophilic phenotype could only be found in 8% of patients in a 2 year study course [89].

**Phenotyping according to omics**

In the recent years, omics-based technologies have been developed in order to identify genes and molecular pathways related to inflammatory and clinical characteristics in asthma [77]. Omics-based technologies include transcriptomics, proteomics and metabolomics.

For the identification of transcriptomic asthma endotypes, the expression of several genes has been analyzed in bronchial epithelial cells and sputum cells of severe asthmatics and many of these genes were associated with T2-high or T2-low inflammation, suggesting which patients would possibly respond to corticosteroid therapy [90-94]. Similarly, studies have investigated the proteomics profile of asthma in different specimens such as BAL [95], bronchial biopsies [96] and sputum supernatants [97]. Different inflammatory phenotypes have been shown to express different inflammatory proteins [78]. Finally, studies on metabolomics (i.e. the exploration of biochemical molecules derived from metabolic processes) using exhaled air, urine, or peripheral blood samples have shown that they could predict sputum eosinophils and corticosteroid response [98, 99].

**Aspirin/NSAID exacerbated respiratory disease (AERD/N-ERD)**

Patients with aspirin (and/or nonsteroidal anti-inflammatory drugs (NSAID)) exacerbated respiratory disease (AERD/N-ERD) comprise approximately 0.6-2.5% of the entire asthma population. In a recent study it has been reported that AERD/N-ERD occurred in approximately 15% of patients with severe asthma [100]. AERD/N-ERD usually develops in the third or fourth decade of life [101] has a male predominance and comprises asthma, chronic rhinosinusitis with nasal polyps, and acute respiratory reactions following the ingestion of aspirin or NSAIDs [102]. The inflammatory mechanism of AERD/N-ERD includes infiltration of inflammatory cells including mast cells, basophils and eosinophils into the airways, producing and secreting high levels of cysteinyl leukotrienes (cysLTs) [103] through upregulation of 5-lipoxygenase and leukotriene (LT)$C_4$ synthase [104, 105]. Furthermore, mast cells also release vasodilating and bronchoconstricting agents including histamine, tryptase and prostaglandin D2 augmenting the leukotriene response [106]. This condition has been associated with genetic single nucleotide polymorphisms in genes encoding CysLT receptor $(R)_1$ and $CysLTR_2$ which influence their transcriptional activity [107]. 24-hour LTE4 urinary levels seem valuable biomarkers of AERD/N-ERD [108].

The first line therapy of AERD/N-ERD comprises avoidance of aspirin and other NSAIDs intake. In line with the underlying mechanism, patients with AERD/N-ERD clearly benefit from treatment with cysLT receptor antagonists (LTRA) such as zafirlukast and montelukast and 5-lipoxygenase inhibitors such as zileuton [109]. Both treatment options have been shown to improve symptoms, quality of life, lung function, use of rescue medication and exacerbations [109, 110]. Alternative treatments such as aspirin desensitization and polypectomy can also be considered

on individual basis [103]. Furthermore, since eosinophilic inflammation plays a pivotal role in AERD/N-ERD, biologics targeting IL-5 may be effective in these patients although efficacy needs to be confirmed and cost-effectiveness compared to the cheaper treatment options [103]. Finally, given the role of PDG2 and its receptors DP1 and CRTH2 in these patients, combinations with DP1 and CRTH2 antagonists might be another promising therapeutic option which needs to be established in future studies [111].

**Obese Asthma**

Obesity is known to cause alteration in lung volumes and airway caliber, and is associated with more severe disease with impaired asthma control and treatment response [112, 113]. This in combination to the observation that airway distribution is influenced more by abdominal fat mass compared to other fat locations leads to the conclusion that airway inflammation per se is not the main cause for the development of asthma in obese asthmatic patients [114]. Several studies have shown that the inflammatory process in obese asthmatic patients is enhanced by adipose hormones such as insulin, leptin and adiponectin [115-117]. Airway inflammation in obese asthmatics can be T2-high or T2-low [118]. Obese asthmatic patients with childhood onset asthma present with increased eosinophilic activity [119], while obese patients with late onset asthma seem to be minimally or non-allergic and develop airway inflammation characterized by a T2-low profile with poor response to corticosteroid therapy [120].

Since Body Mass Index affects treatment outcomes in asthma [113], there is an unmet need for the development of special therapeutic options for this phenotype. Both weight loss by caloric restrictions in combination with exercise or

bariatric surgery have been shown to improve asthma control and to reduce exacerbation risk [121-124] in obese asthmatics. In obese mice increased levels of acetylcholine within the lungs highlight the possible use of antimuscarinic agents as adjuvant therapy in the treatment of asthma in obese patients [125]. Finally, leukotrienes have been shown to be increased in obese asthmatics [126]. This observation, in addition to the fact that impaired response to corticosteroids is not accompanied by an impaired response to LTRA in a post-hoc analysis [113], leads to the conclusion that these agents might be a useful therapeutic option for this asthma phenotype.

**Persistent airway obstruction**

More than 50% of patients with severe refractory asthma develop irreversible airway obstruction [127, 128]. Patients are characterised as having persistent airflow obstruction if $FEV_1$ values are permanently <70% predicted at all visits, or if having only a single value of $FEV_1$ between 70% and 75% predicted during a 1-year follow up [128].

The main cause of the development of fixed airway obstruction in asthmatic patients is airway remodelling mainly associated with epithelial cell hyperplasia, goblet cell metaplasia, increase of ASM, airway wall fibrosis and ongoing Th1 (expressed as increased levels of IL-12 and IFN-γ) and Th2 (expressed as increased levels of IL-13) inflammation, as well as increased levels of neutrophils and eosinophils within the airways [128, 129]. Although patients with severe asthma and persistent airflow obstruction have increased ASM they do not present specific characteristics on high-resolution computed tomographic scans or sputum analysis [128].

Studies have shown that patients with persistent airway obstruction are predominantly male, more often exposed to cigarette smoke and usually non-atopic [130]. Furthermore, they seem to have longer disease duration, more impaired lung function (lower $FEV_1$, FVC, $FEV_1$/FVC ratio and DLCO, higher FRC values), increased bronchial hyperresponsiveness, higher FeNO levels, increased sputum eosinophil and neutrophil counts and receive more intense treatment [130, 131]. Another important observation is that the majority of patients with persistent airway obstruction seem to fulfil the criteria for SRA in contrast to a small minority of patients without persistent airflow obstruction [131].

Increased ASM thickness is expected to lead to increased airway wall tension and more excessive airway narrowing and one would expect that adequate bronchodilation and anti-inflammatory therapy should be able to reverse this obstruction. Although therapy with ICS decreases airway wall thickness, asthmatic patients with persistent airway obstruction do not fully respond to treatment [128].

The decreased response to therapy with anti-inflammatory drugs in patients with persistent airway obstruction has led to the use of BT for the reduction of airway smooth muscle [75] and downregulation of structural abnormalities involved in airway narrowing and bronchial reactivity, particularly ASM, neuroendocrine epithelial cells, and bronchial nerve endings [132]. Clinical trials of BT in patients with moderate to severe asthma have reported improvement in asthma control, asthma related quality of life and reduction in the number of exacerbations [74, 75, 133].

**Exercise induced bronchoconstriction**

The term exercise-induced bronchoconstriction (EIB) is used to describe the transient and reversible narrowing of the lower airways that follows vigorous

exercise [134]. This condition occurs in approximately 90% of asthmatic subjects [135] and studies have shown that asthmatic patients with more severe or poorly controlled asthma are more likely to exhibit EIB compared to those with less severe or well-controlled disease [136].

Two main theories have been used to explain the mechanism of bronchospasm during exercise, the thermal theory and the osmotic theory. The thermal theory, proposes that the cooling of the airway, which occurs as a result of water loss, causes vasoconstriction in bronchial vasculature. On rewarming, airway narrowing will occur due to the mechanical effects of vascular engorgement, vascular leakage, and edema of the airway wall [137]. Thus, in this scenario, airway narrowing would occur as a direct consequence of vascular events and would be unrelated to mediator release or airway smooth muscle contraction. On the other hand, the osmotic theory proposes that airway water loss results in increased osmolarity of the airway surface liquid, which extends to include the airway epithelial cells and submucosa. This hyperosmolar environment activates cellular mechanisms to release various mediators which in turn cause airway smooth muscle contraction and subsequent airway narrowing [137].

The diagnosis of EIB requires documentation of changes in lung function after exercise.[138]. Typical diagnostic tests include either indirect challenge tests such as exercise challenge tests, eucapnic voluntary hyperpnea and inhalation of hyperosmolar aerosols (4.5% saline or dry powder mannitol) [139, 140].

The treatment of EIB can be divided in two major categories the non-pharmacologic treatment and the pharmacologic treatment. Non pharmacologic options for the management of EIB include pre-exercise warm up, the use of heat

exchange masks and nutritional methods such as intake of high dose of omega 3 fish oil supplementation [139-141]. Pharmacologic therapy includes short-acting b2-agonists (SABAs), long-acting b2-agonists (LABAs), leukotriene receptor antagonists (LTRAs), and inhaled corticosteroids (ICSs). Short acting beta 2 agonists (such as salbutamol) are recommended as first line treatment both as prevention and for the relief of acute symptoms. They should be administered shortly before exercise (approximately 15 min) since they have a peak action in 15-60 min which lasts approximately 4 hours [139]. However, they may fail to prevent bronchoconstriction in 15–20% of patients with asthma and when used daily it leads to tolerance, due to desensitization of the β2-receptors on mast cells and airway smooth muscle [140]. Long acting beta 2 agonists have also been shown to be effective for the prevention of EIB; however, they should only be used with a concomitant use of a controller medication, such as inhaled corticosteroids (ICS) [139]. Leukotriene receptor antagonists have been shown to have a persistent benefit against EIB. Montelukast has an onset of action within 2 hours and continues to have a preventive benefit for up to 24 hours after a single oral dose [139].

**Discussion**

As we are heading towards personalised therapy, it is important to deeply understand the underlying pathophysiological mechanisms of asthma phenotypes and/or endotypes in order to achieve optimal treatment goals. Asthma phenotypes and possible therapeutic interventions are summarized in table 1. In clinical practice, the dichotomous approach to low and high T2 response is mainly based on the assessment of eosinophilic inflammation as reflected by blood eosinophil counts. Although the presence of atopy strengthens the T2 response, at the same time,

atopic patients with low eosinophilic profile are excluded. If we consider how many patients in our daily clinical practice are atopic without eosinophils, the question that rises is whether the aforementioned approach is realistic or not. A proposed treatment algorithm complementing the T2 high and T2 low characterization is provided in Figure 1. Applying this algorithm, patients with severe asthma are assessed on the basis of eosinophilic inflammation using either routine-based parameters or some non-invasive ones such as induced sputum. At the same time, the presence of other characteristics such as allergy, obesity, chronic rhinosinusitis plus minus nasal polyposis, aspirin sensitization and persistent airway obstruction, that may need additional targeted approach, are also considered.

Although clinical presentation of severe asthma is more or less similar in the majority of patients, different underlying inflammatory mechanisms have been identified, resulting in different response to treatment. Although severe asthma should be always managed targeting to the type of airway inflammation, many limitations exist mainly attributed to the lack of a clear inflammatory phenotype, to the low availability and the time-consuming process of the technique of induced sputum and finally to the absence of an established protocol in order to titrate our treatment strategies. The use of relevant biomarkers is very promising for the identification of different asthma phenotypes which may best benefit from targeted therapies. If we overcome these limitations and consider that many endotypes may offer us the opportunity to apply the above techniques, we can then consider them as necessary options for the future management of the disease. At the moment, our approach, which we have to acknowledge that is mostly opinion based, mainly relies

on simplicity in order to clearly identify phenotypes or endotypes and establish treatment strategies.

Finally, we have to admit that although important steps in the field of precision medicine have been made, still there are several unmet needs which have to be satisfied for the successful implementation of targeted therapies into routine clinical care including the treatment of different types of exacerbations occurring in the different asthma phenotypes. One of the main limitations is the lack of specific sensitive and affordable biomarkers which will allow the clear characterization of the patients' phenotype and will allow the clear choice of a targeted molecular therapy with minimal or no overlap between different options.

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**Table 1: Asthma phenotypes and possible therapeutic interventions.**

| Phenotype | Characteristic | Therapeutic interventions | References |
|---|---|---|---|
| ***Inflammatory phenotypes*** | | | |
| Eosinophilic (40-60% of the asthmatic population) | Sputum Eo≥2-3% | Anti-IgE (for allergic asthma)<br>Anti-IL-5<br>Anti-IL4/IL13R | [31]<br>[19, 32, 33]<br>[30, 34] |
| Neutrophilic (5-22% of the asthmatic population) | Sputum Ne≥61% | Macrolides<br>Bronchial thermoplasty | |
| Paucigranulocytic (17-48% of the asthmatic population) | Both Sputum Eo<2% and Ne<61% | | |
| Mixed | Both Sputum Eo≥2-3% and Ne≥61% | | |
| ***Phenotypes based on -omics*** | Transcriptomics: expression of genes in bronchial epithelial cells and sputum cells.<br>Proteomics: Expression of proteins in specimens such as BAL bronchial biopsies and sputum supernatants.<br>Metabolomics: Exploration of biochemical molecules derived | | [90-94]<br>[95] [96] [97]. |

| | | | |
|---|---|---|---|
| | from metabolic processes | | [98, 99] |
| ***Aspirin exacerbated respiratory disease (AERD)*** | Asthma symptoms exacerbate by aspirin and NSAIDs | LTRAs<br>5-lipoxigenase inhibitors<br>Aspirin desensitization<br>Polypectomy | [109, 110] |
| ***Asthma in obese subjects*** | Asthma present in obese patients | Weight loss (caloric restriction and/or bariatric therapy) | [121-124] |
| ***Persistent airway obstruction*** | $FEV_1$ values are permanently <70% predicted at all visits, or if having only a single value of $FEV_1$ between 70% and 75% predicted during a 1-year follow up | Bronchial Thermoplasty | [74, 75, 132, 133] |
| ***Exercise induced bronchoconstriction*** | the transient and reversible narrowing of the lower airways that follows vigorous exercise | Non-pharmacologic:<br>-pre-exercise warm up<br>-use of heat exchange masks<br>-nutritional methods.<br>Pharmacologic:<br>-short-acting b2-agonists<br>-long-acting b2-agonists<br>-leukotriene receptor antagonists<br>-inhaled corticosteroids | [139-141] |

Abbreviations: Eo: eosinophils, Ne: neutrophils, NSAIDs: Non-steroid anti-inflammatory Drugs, LTRAs: Leukotriene Receptor Antagonists,

**Figure legends**

Figure 1: Severe asthma algorithm approach: A simple approach.

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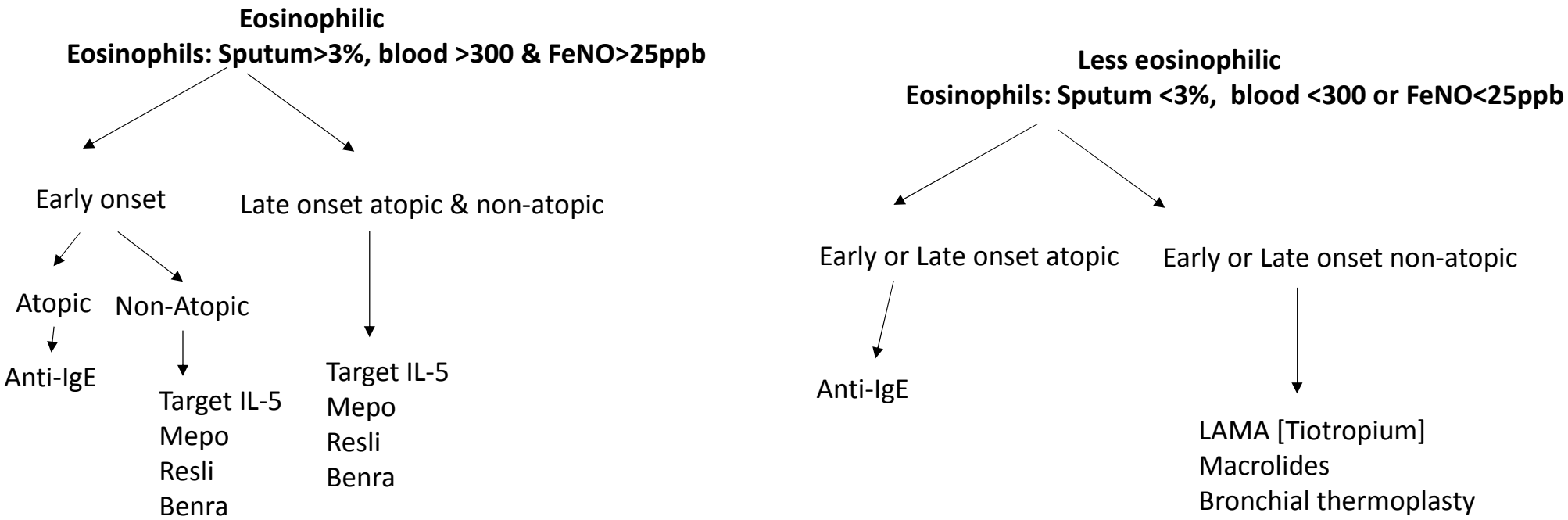

**Highlights YRMED-D-18-00319**

- Severe asthma is a heterogeneous and complex disease with variable response to standard treatment.
- As a heterogeneous disease, severe asthma can present with many overlapping clinical phenotypes.
- Personalised approach is based on the different underlying pathophysiological mechanisms of severe asthma.
- A simpler approach may clearly identify phenotypes or endotypes and establish treatment strategies.