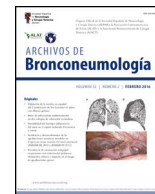




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## Review Article

# Airway Remodeling in Asthma: Mechanisms, Diagnosis, Treatment, and Future Directions

1 Angelica Tiotiu Cepuc<sup>a,b,\*</sup>, Paschalis Steiropoulos<sup>c</sup>, Silviya Novakova<sup>d</sup>, Denislava Nedeva<sup>e</sup>,  
2 Plamena Novakova<sup>f</sup>, Herberto Chong-Neto<sup>g</sup>, Guillermo Guidos Fogelbach<sup>h</sup>, Krzysztof Kowal<sup>i</sup>

3 <sup>a</sup> Department of Pulmonology, University Hospital Saint-Luc, Brussels, Belgium

4 <sup>b</sup> Pole Pneumology, ENT, and Dermatology – LUNS, Institute of Experimental and Clinical Research (IREC), UCLouvain, Brussels, Belgium

5 <sup>c</sup> Department of Pulmonology, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Greece

6 <sup>d</sup> Department of Allergology, University Hospital “Sv. Georgi” Plovdiv, Bulgaria

7 <sup>e</sup> Clinic of Asthma and Allergology, UMBAL Alexandrovska, Medical University Sofia, Sofia, Bulgaria

8 <sup>f</sup> Department of Allergy, Medical University Sofia, Sofia, Bulgaria

9 <sup>g</sup> Division of Allergy and Immunology, Complexo Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Brazil

10 <sup>h</sup> School of Medicine, ENMH, Instituto Politecnico Nacional, Mexico City, Mexico

11 <sup>i</sup> Department of Experimental Allergology and Immunology and Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland

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## ABSTRACT

Airway remodeling (AR) with chronic inflammation, are key features in asthma pathogenesis. AR characterized by structural changes in the bronchial wall is associated with a specific asthma phenotype with poor clinical outcomes, impaired lung function and reduced treatment response. Most studies focus on the role of inflammation, while understanding the mechanisms driving AR is crucial for developing disease-modifying therapeutic strategies.

This review paper summarizes current knowledge on the mechanisms underlying AR, diagnostic tools, and therapeutic approaches. Mechanisms explored include the role of the resident cells and the inflammatory cascade in AR. Diagnostic methods such as bronchial biopsy, lung function testing, imaging, and possible biomarkers are described. The effectiveness on AR of different treatments of asthma including corticosteroids, leukotriene modifiers, bronchodilators, macrolides, biologics, and bronchial thermoplasty is discussed, as well as other possible therapeutic options.

AR poses a significant challenge in asthma management, contributing to disease severity and treatment resistance. Current therapeutic approaches target mostly airway inflammation rather than smooth muscle cell dysfunction and showed limited benefits on AR. Future research should focus more on investigating the mechanisms involved in AR to identify novel therapeutic targets and to develop new effective treatments able to prevent irreversible structural changes and improve long-term asthma outcomes.

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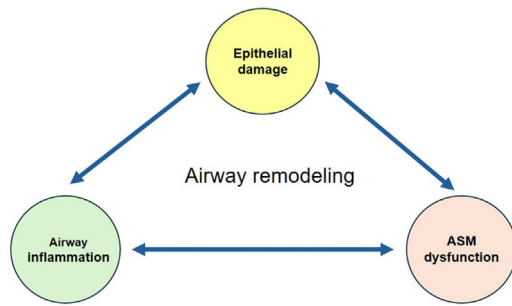
## Introduction

Asthma is a chronic airway inflammatory disease characterized by typical respiratory symptoms (cough, wheeze, chest tightness, shortness of breath) that vary over time and in intensity associated with variable expiratory airflow limitation. In some patients with long-lasting asthma, airflow obstruction becomes persistent and incompletely reversible due to pathological airway remodeling (AR).<sup>1,2</sup>

AR is a complex feature of asthma that involves long-term changes of airway architecture such as hyperplasia of the smooth muscles, subepithelial collagen deposition with increased thickness of the reticular basement membrane (RBM), disruption of the epithelial barrier integrity with metaplasia of goblet cells inducing mucus hyperproduction, and angiogenesis.<sup>3,4</sup> AR pathogenesis is not fully understood. Until recently, it was thought that it is caused by chronic airway inflammation.<sup>5</sup> However, AR is not only a feature of late-onset asthma, because structural changes were found in bronchial biopsies from pre-school children with severe wheezing and a murine model with neonatal inhaled allergen-disease.<sup>6–8</sup> These findings suggest that AR may occur early in the disease, and could be a triggering process, rather than a secondary event.<sup>9,10</sup> A

\* Corresponding author.

E-mail address: angelica.tiotiu@yahoo.com (A.T. Cepuc).



**Fig. 1.** Main contributors to airway remodeling in asthma. ASM: airway smooth muscle.

genetic predisposition is also suggested.<sup>4</sup> AR is associated with poor clinical outcomes, impaired lung function, lower response to treatment, and altered quality of life (measured by Asthma Quality of Life Questionnaire – AQLQ) in asthma patients.<sup>11</sup> Even though the degree of remodeling correlates with asthma severity, alterations of the bronchial wall are also present in mild disease.<sup>12,13</sup> Like inflammation, AR in asthma is heterogeneous, varies between individuals, and may contribute to asthma phenotypes and endotypes.<sup>14</sup>

As the presence of AR is associated with more severe asthma (SA) and poor response to treatment, targeting this component of the disease with early diagnosis and prevention could improve clinical outcomes and patients' AQLQ score.<sup>13</sup> This review summarizes current knowledge on the mechanisms underlying AR in asthma, the diagnostic tools, the clinical phenotypes and the possible therapeutic approaches in the aspect of personalized medicine.

## Mechanisms

AR is the result of complex interaction between the airway resident cells (epithelial cells, smooth muscle cells, fibroblasts, neuronal cells, endothelial cells), the inflammatory cells (dendritic cells – DCs, eosinophils, neutrophils, mast cells – MCs, macrophages, lymphocytes and innate lymphoid cells – ILC), and many humoral components (cytokines, enzymes, and growth factors)<sup>2,7,10</sup> (Figs. 1 and 2).

### AR as Secondary Event of Inflammation

According to the “inflammatory theory”, the airway epithelial cells (AECs) are the “initiators” of the process.<sup>10,15</sup> Following exposure to allergens, microbial proteins, and air pollutants, injured AECs release alarmins (e.g. IL-33, IL-25, TSLP) that activate DCs, ILC2, T helper 2 lymphocytes (Th2), MCs, and macrophages, which contribute to downstream inflammation.<sup>5,15</sup> In addition, environmental injuries may induce AECs apoptosis, with paracrine secretion of transforming growth factor- $\beta$  (TGF- $\beta$ ) which initiates tissue regeneration to restore homeostasis. However, persistent, and prolonged tissue stimulation by growth factors can lead to pathological AR seen in asthma.<sup>10</sup>

The alarmins could directly induce collagen production by lung fibroblasts. IL-25 promotes lung fibroblasts proliferation while IL-33 induces the expression of fibronectin. The consequent accumulation of extracellular matrix (ECM) proteins leads to subepithelial RBM thickening that occurs early in the pathogenesis of asthma.<sup>15</sup>

The three alarmins promote eosinophilic inflammation by activating ILC2 and Th2 via DCs, both sources of IL-4, and IL-13, that increase mucus production, collagen synthesis and deposition, airway smooth muscle (ASM) cell contraction and proliferation, and fibroblast-to-myofibroblast transition (FMT).<sup>15,16</sup> Eosinophils release various mediators including TGF- $\beta$  that can directly activate

the AECs and mesenchymal cells.<sup>15</sup> Alarmins trigger the production of TGF- $\beta$  by macrophages and stimulate ASM proliferation. Activated macrophages release matrix metalloproteinases (MMPs) that can alter the ECM structure.<sup>10,15</sup> During allergic response, MCs secrete mediators (e.g. histamine, prostaglandin D<sub>2</sub>, tryptase), cytokines (e.g. TSLP, IL-33, IL-13), and vascular growth factors that induce fibroblast, endothelial, and epithelial cell proliferation promoting AR.<sup>13</sup> In non-allergic asthma, AECs stimulate the production of Th17 cytokines inducing neutrophilic inflammation and TGF- $\beta$  production with accumulation of fibrotic matrix components. The immune cells are “amplifiers” of AR.<sup>10</sup>

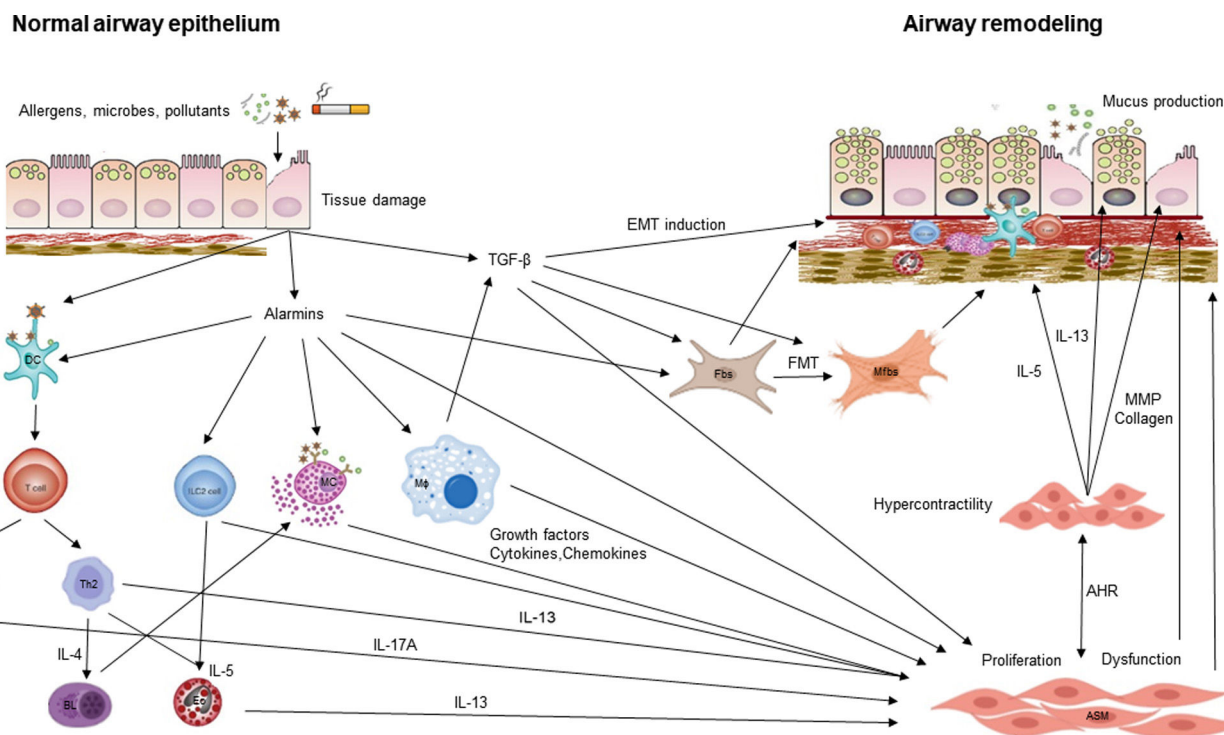
The epithelial–mesenchymal transition (EMT), a key feature of AR, is a biological process allowing AECs to assume a mesenchymal cell phenotype. That includes increased migratory capacity, invasiveness, resistance to apoptosis, and production of ECM components, contributing to airway wall fibrosis.<sup>10</sup> This process is upregulated by growth factors (e.g. TGF- $\beta$ ), cytokines and mediators (e.g. IL-4, IL-24, MMPs) secreted by resident and inflammatory cells.<sup>17–21</sup>

Subepithelial fibrosis is mediated by submucosal resident fibroblasts that proliferate and differentiate into myofibroblasts through the process of FMT. Myofibroblasts are mesenchymal cells with contractile and secretory abilities (e.g. collagen, fibronectin, MMPs, growth factors). TGF- $\beta$  plays a central role in the induction of FMT in asthma, but interleukins (e.g. IL-4, IL-5, IL-13, IL-17, IL-25, IL-33), chemokines (eotaxin, periostin), as well as mechanical forces and ECM proteins could also influence this process.<sup>22</sup>

ASM mass is increased in both large and small airways in asthma due to cells hyperplasia. The ASM layer thickness correlates positively with the severity of asthma. Additional immigration of myofibroblasts contributes to the rise of ASM layer. These processes are triggered by growth factors (e.g. TGF- $\beta$ ), cytokines (e.g. TSLP), components of the ECM, and chemokines.<sup>23</sup> ASM cells from asthma patients exhibit increased metabolism, and proliferation which can lead to changes in mechanical capabilities, increased airway stiffness, and the formation of mucosal folds.<sup>14</sup> ASM cells can also contribute to airway inflammation through the release of cytokines and chemokines (e.g. IL-5, IL-13, eotaxin), regulate ECM via the secretion of MMPs, collagen type I, and perlecan, which in turn, may promote the ASM proliferation. MCs infiltration is increased in ASM in asthma patients, and their number correlates with the degree of airway hyperresponsiveness (AHR).<sup>13</sup> In this model, fibroblasts and ASM cells are “effectors” of AR in asthma.<sup>10</sup>

### AR as Primary Event

ASM is the cell responsible for generation of airway tone and contraction. Enhanced contractility of ASM was found in asthma patients due to abnormalities of calcium homeostasis and/or sensitization and altered airway innervation. Increased ASM contractility contributes to AHR.<sup>24</sup> AR might be initiated in the absence of inflammation, following bronchoconstriction in response to stimuli.<sup>2,7</sup> During bronchoconstriction, the airway epithelium is subjected to excessive mechanical forces causing AECs damage that leads to previous described effects contributing to AR (e.g. release of TGF- $\beta$  promoting subepithelial fibrosis by fibronectin collagen type III and V deposition, FMT, ASM cells hyperplasia and mucus hypersecretion due to goblet cell metaplasia). Bronchoconstriction stimulates epithelium to release IL-6, IL-8, and monocyte chemoattractant protein-1, which act as mitogens for ASM cells.<sup>13</sup> Several data suggests that mitochondrial dysfunction could play a role in ASM remodeling in asthma.<sup>8,25</sup>



**Fig. 2.** Mechanisms involved in asthma airway remodeling. AHR: airway hyperresponsiveness, ASM: airway smooth muscle, BL: B lymphocyte, DC: dendritic cell, Eo: eosinophil, EMT: epithelial mesenchymal transition, Fbs: fibroblast, FMT: fibroblast–myofibroblast transition, IL: interleukin, ILC2: innate lymphoid cell type 2, Mφ: macrophage, MC: mast cell, MMP: matrix metallo-proteinase, Mfbs: myofibroblast, Ne: neutrophil, Th2: T helper 2 cell, Th17: T helper 17 cell, TGF-β: transforming growth factor beta.

**Diagnosis Tools**

**Bronchial Biopsy**

The gold standard of AR diagnosis requires bronchial biopsy by fiberoptic bronchoscopy allowing to the direct examination of the tissue (Fig. 4). However, this method is invasive and reflects mostly the proximal airways rather than small airways, so it is not recommended to be performed routinely in clinical practice.<sup>2,10</sup> A recent study in asthma adults identified different clusters according to the structural changes on bronchial biopsies. The cluster with high ASM mass (19% of studied patients) was characterized by sputum eosinophilia, elevated total serum IgE levels, increased prevalence of positive skin test for *Aspergillus* sp, low lung function, important AHR, and moderate therapeutic pressure. The particularities of the cluster with high RBM thickness (31% of patients) were: increased prevalence of atopy, high total serum IgE levels, sputum eosinophilia, moderate decrease in lung function, elevated exhaled fraction of nitric oxide (FeNO) despite maximal daily doses of inhaled corticosteroids (ICS), and great AHR.<sup>26</sup> Asthma patients with ASM area >26.6% had worse asthma control, high rate of exacerbations per year and increased weekly use of reliever medication.<sup>25</sup>

**Biomarkers**

Currently there are no specific biomarkers for the assessment of AR in clinical practice. Blood eosinophilia was identified as a risk factor for airflow obstruction in asthma and predictive for enhanced longitudinal decline in lung function.<sup>27</sup> Clinical studies showed increased levels of eosinophils in blood, sputum, and bronchoalveolar lavage fluid in patients with irreversible airway obstruction (IRAO) compared to those with reversible airway obstruction.<sup>28,29</sup> FeNO, another biomarker of T2-asthma, is correlated with greater

AHR in asthmatic children and adults.<sup>27</sup> Elevated serum levels of periostin were found in asthma adults with fixed and more severe airflow obstruction, while its expression in bronchial biopsies is associated with enhanced lung function decline.<sup>27–29</sup> Serum periostin seems to be more useful than blood eosinophils or FeNO for assessing AR in asthmatics, even in those well-controlled.<sup>30,31</sup> Patients with IRAO have high serum levels of fibrinogen and TGF-β, but their potential as biomarkers of AR should be better investigated.<sup>28,29</sup>

**Lung Function Tests**

Asthma diagnosis is usually confirmed when evidence of variable expiratory airflow limitation assessed by spirometry or measure of Peak Expiratory Flow (PEF), over time, and in magnitude. Spirometry testing allowed to the measure of the forced expiratory volume per second (FEV<sub>1</sub>) and the ratio of FEV<sub>1</sub> to forced vital capacity (FEV<sub>1</sub>/FVC). Decrease of these parameters indicates expiratory airflow limitation. Responsiveness (previously called “reversibility”) should be tested if suspicion of asthma. Improvement from baseline in FEV<sub>1</sub> or FVC by ≥12% and 200 mL, measured within minutes after inhalation of rapid-acting bronchodilator, or weeks after the introduction of ICS was considered longtime as a positive responsiveness test, but recently the cut-off has been changed by >10% of the patient’s predicted value. Sometimes, a bronchial provocation test is needed to assess AHR.<sup>1</sup>

Some asthma patients develop IRAO (FEV<sub>1</sub>/FVC <0.7 and FEV<sub>1</sub> <80%) due to the presence of AR.<sup>24,25</sup> They have a particular clinical phenotype of “asthma with persistent airflow limitation”<sup>1</sup> (Fig. 3). IRAO is present in 55–60% of patients with SA.<sup>10</sup>

PEF measurement is not useful for the diagnosis of AR. Spirometry assesses the severity of airflow obstruction, but it not directly detects AR. However, certain spirometry findings like the persistent airflow limitation despite treatment, the reduced lung function,

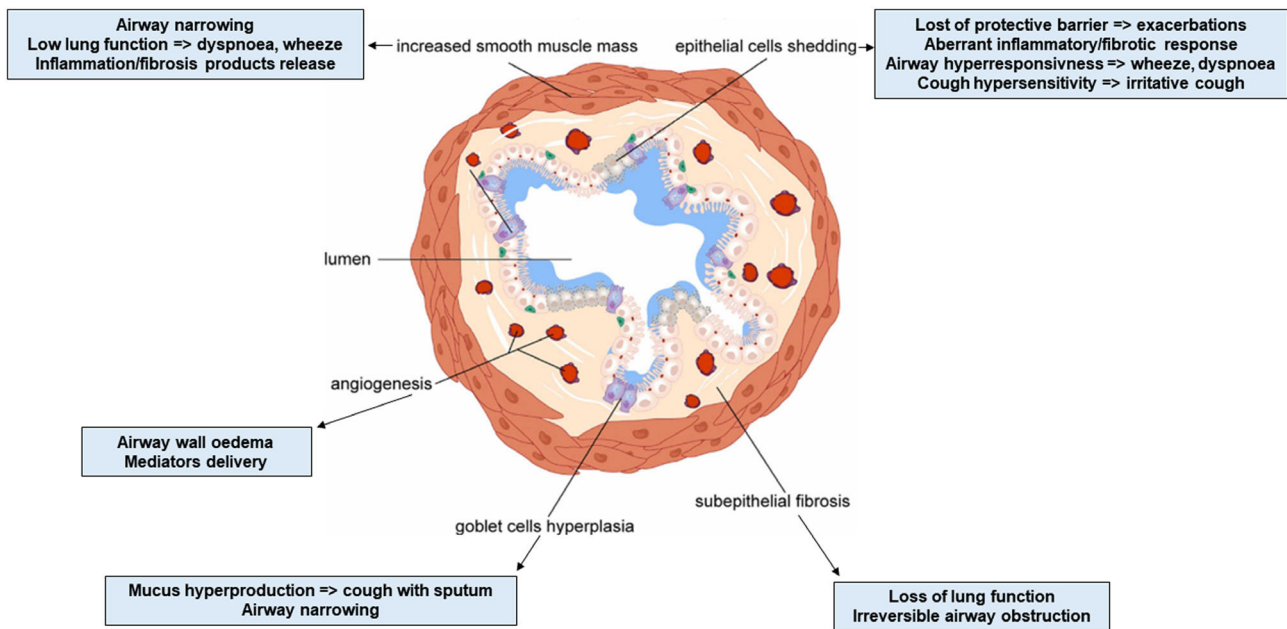


Fig. 3. Main structural airway remodeling features correlated with clinical characteristics of asthma.

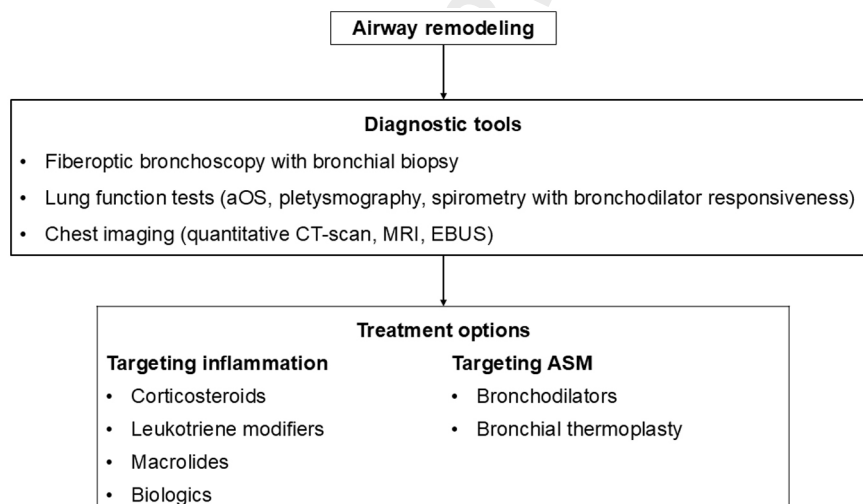


Fig. 4. Summary of current diagnostic tools and therapeutic options of airway remodeling in asthma. aOS: airway oscillometry, CT: computed tomography, MRI: magnetic resonance imaging, EBUS: endobronchial ultrasound.

220 and the decreased responsiveness to bronchodilator medications  
 221 may suggest the presence of AR in severe or long-standing asthma.  
 222 Spirometry is useful for monitoring disease progression in asthma,  
 223 including AR development over time, and helps physicians to  
 224 prevent this feature by adjusting the treatment.<sup>1</sup> In addition to  
 225 spirometry, the plethysmography assesses the airway resistance  
 226 (Raw) directly related to AR and the presence of indirect signs of  
 227 airway obstruction such as pulmonary hyperinflation.<sup>29,32,33</sup> The  
 228 bronchial lumen area correlates directly with bronchial obstruction  
 229 parameters (FEV<sub>1</sub>, forced mid-expiratory flow FEF<sub>25-75</sub>) and  
 230 inversely with residual volume and Raw.<sup>33</sup> Airway oscillometry  
 231 (aOS) is particularly useful in asthma. By measuring Raw, reactance,  
 232 and impedance across a range of frequencies, aOS provides  
 233 a more comprehensive evaluation of airway function compared to  
 234 traditional spirometry. Increased Raw and respiratory impedance  
 235 correlate with the degree of AR in asthma and could detect early  
 236 changes in airway function even before airflow limitation.<sup>34</sup> Oscil-  
 237 lometry bronchodilator response also seems more sensitive than

238 those assessed by spirometry and should be performed before  
 239 labeling people with the term IRAO.<sup>35</sup> Persistent AHR has been  
 240 identified as a risk factor for longitudinal decline of FEV<sub>1</sub> in asthma  
 241 patients even in those well-controlled by ICS.<sup>35</sup> Early identification  
 242 of AHR by bronchial provocation tests allows for timely therapeutic  
 243 intervention and prevention of AR.<sup>1</sup>

244 Several factors were identified as associated with IRAO such  
 245 as male gender, long disease duration, cigarette smoking, uncontrolled  
 246 asthma, sputum eosinophils and neutrophils, and high therapeutic  
 247 pressure including oral corticosteroids (OCS). An Asthma Control  
 248 Questionnaire score of 2.36 could identify IRAO with a high sensitivity  
 249 (72%) and specificity (77%).<sup>28</sup>

250 *Imaging*

251 Routinely performed chest X-ray examination is not helpful to  
 252 evaluate AR in asthma patients. Its clinical value is restricted to

253 identify asthma complications or concomitant disorders such as  
254 pneumonia or pneumothorax.

255 The airways have been reliably examined with computed  
256 tomography (CT) scans from more than 20 years.<sup>37,38</sup> Since its  
257 introduction, multidetector computed tomography (MDCT) has  
258 proved to be particularly useful in the evaluation of AR in asth-  
259 matic patients.<sup>39–41</sup> By applying minimal radiation levels, the  
260 new-generation MDCT provides better resolution than helical  
261 CT with acquisition of multiple cross-sectional slices as thin  
262 as 0.60–0.75 mm without interslice gaps, in shorter time, dur-  
263 ing inspiratory and expiratory phases, with the possibility to  
264 extract quantitative data.<sup>42–45</sup> Quantitative CT (qCT) can evaluate  
265 bronchial thickness (lumen diameter – LD and area – LA, bronchial  
266 wall thickness – WT and area – WA), the presence of mucous plugs  
267 in the airways, lung hyperinflation and air trapping (e.g. identifi-  
268 cation of low-attenuation areas, measure of lung density).<sup>39,46–49</sup>  
269 The features of AR observed in qCT images show strong cor-  
270 relations with pathological and functional examinations.<sup>29,50,51</sup>  
271 Analysis of qCT allowed to identify distinct asthma phenotypes with  
272 different clinical outcomes. The more advanced AR on qCT is asso-  
273 ciated with low lung function, high exacerbation rate, and worse  
274 response to standard therapy.<sup>29,47,52</sup> Mucus plugging on CT-scan  
275 is linked to T2-inflammation, more severe asthma, frequent exac-  
276 erbations and poor lung function.<sup>53,54</sup> Positive correlations were  
277 found between WA% ≥ 50% on CT-scan and increased peripheral  
278 resistance and reactivity measured by aOS.<sup>55</sup> Recent longitudinal  
279 studies demonstrated that qCT can help in selecting asthmatics  
280 prone to irreversible loss of lung function with time and assist in the  
281 evaluation of response to biologics, becoming a useful diagnostic  
282 tool for personalized medicine in asthma management.<sup>46,56,57</sup>

283 Compared to CT-scan, magnetic resonance imaging (MRI)  
284 provides superior soft-tissue contrast, without patient radia-  
285 tion exposure.<sup>58,59</sup> Fast imaging protocols are based on breath  
286 hold acquisitions or triggering/gating to compensate for motion  
287 artifacts.<sup>59</sup> However, MRI has lower spatial resolution than qCT,  
288 so non-contrast-enhanced MRI is not very useful for the evaluation  
289 of subtle changes in airway structure seen in asthma patients.<sup>58</sup>  
290 The application of hyperpolarized gases with MRI allows to direct  
291 assessment of ventilation heterogeneity and quantitative measure-  
292 ment of terminal airway, that correlate with AR. Serial imaging  
293 can evaluate disease progression and response to therapy over  
294 time.<sup>58–60</sup>

295 The endobronchial ultrasound technique (EBUS) is also useful  
296 for the assessment of AR in asthma patients.<sup>61</sup> EBUS allows the  
297 detailed analysis of the bronchial wall structures distinguishing dif-  
298 ferent layers. The inner layers contain the epithelium, submucosa,  
299 and ASM while the outer layers correspond to cartilage.<sup>61,62</sup> In dis-  
300 tal no cartilaginous airways EBUS can visualize the three layers of  
301 the bronchial wall.<sup>62</sup> The EBUS may be useful for asthma patients  
302 to evaluate wall changes after bronchial thermoplasty (BT).<sup>63</sup> How-  
303 ever, EBUS is an invasive method, requires an expert bronchoscopy  
304 skill, and allows for local evaluation of the airways.

305 The role of other imaging methods such as optical coherence  
306 tomography or positron emission tomography in the evaluation of  
307 AR should be determined.<sup>60,64</sup>

## 308 Treatment

### 309 Corticosteroids

310 Corticosteroids are the cornerstone of treatment in asthma.<sup>1</sup>  
311 Several clinical data showed that inhaled corticosteroids (ICS)  
312 decreased RBM thickness and collagen type III deposition in  
313 bronchial biopsies in asthma patients if administered for more  
314 than 6-weeks.<sup>65–68</sup> A greater effect was observed after 2-years of

315 treatment with a high-dose of budesonide, suggesting a possible  
316 dose-dependent, long-term effect.<sup>68</sup> This benefit was not con-  
317 firmed by all studies with ICS, neither after 2-weeks treatment with  
318 OCS.<sup>69–72</sup>

319 The data about the effect of corticosteroids on the airway  
320 epithelial damage are also divergent. Several experimental studies  
321 suggested that corticosteroids may contribute to AR by inducing  
322 AECs apoptosis, while others demonstrated that this treatment  
323 restored the integrity of epithelial cell monolayers through the  
324 redistribution of tight junction proteins.<sup>73–75</sup> Bronchial biopsies  
325 from asthmatics treated 10-years with ICS showed a significant  
326 decrease in the number of inflammatory cells, with small focal areas  
327 with non-ciliated cells and persistence of squamous cell meta-  
328 plasia in some patients, suggesting partial recovery of epithelial  
329 damage.<sup>76</sup>

330 In an animal model, a single dose administration of beclometha-  
331 sone caused acceleration of the mucus release from goblet cells  
332 probably due to overstimulation.<sup>77</sup> Other clinical and experimental  
333 studies from asthma patients treated longer time with ICS demon-  
334 strated an increase in the number of ciliated cells and a reduction  
335 of goblet cell hyperplasia suggesting a possible time-dependent  
336 effect.<sup>78,79</sup>

337 On asthma patients, a 6-months treatment with inhaled  
338 beclomethasone dipropionate decreased both vessel number and  
339 percent vascularity within the lamina propria, modifications asso-  
340 ciated with changes in collagen III thickness.<sup>80</sup> Another study  
341 showed a significant reduction in the vascular component of AR  
342 only in asthma patients receiving high-dose inhaled fluticasone  
343 propionate after 6-weeks of treatment.<sup>81</sup>

344 Despite undeniable evidence of ICS effectiveness on reducing  
345 AHR, the therapeutic index is not the same for all products and  
346 some asthma patients under treatment continue to have airflow  
347 obstruction.<sup>65,69,82–84</sup> In addition, the long-term use of high-dose  
348 ICS is associated with potential systemic side effects.<sup>85</sup>

### 349 Beta-agonists

350 Beta-agonists are vital for alleviating asthma symptoms by  
351 relaxing ASM.<sup>1</sup> Experimental data suggests that long acting  $\beta$ 2-  
352 agonists (LABA) have no impact on ASM cells hyperplasia in  
353 asthma patients, but the association ICS-LABA decreased goblet cell  
354 metaplasia.<sup>86,87</sup> A clinical study showed that salmeterol addition in  
355 asthmatics already receiving ICS, reduced vessels density in lamina  
356 propria after 3-months of treatment.<sup>88</sup>

### 357 Anticholinergics

358 Studies on animal models suggested that tiotropium admin-  
359 istration could reduce AHR, mucus production, thickness of  
360 ASM, subepithelial fibrosis, and goblet cell metaplasia.<sup>89–91</sup> Sev-  
361 eral clinical data showed that addition of tiotropium in asthma  
362 patients treated with ICS-LABA significantly decreased airway  
363 WA and WT on CT-scan ( $p < 0.05$  for both), and improved air-  
364 flow obstruction, while glycopyrronium offers a better protection  
365 against methacholine-induced bronchoconstriction than placebo  
366 ( $p < 0.002$ ).<sup>92–94</sup>

### 367 Leukotriene Modifiers

368 In animal models, leukotrienes receptor antagonists (LTRA)  
369 showed a positive impact on AHR, goblet cell hyperplasia,  
370 EMT, subepithelial fibrosis, ASM hyperplasia by inhibiting TGF- $\beta$   
371 signaling.<sup>95–101</sup> Zileuton, a leukotriene synthesis inhibitor, reduced  
372 ASM mass and ECM deposition in an animal model.<sup>102</sup> LTRA  
373 improve AHR in asthma patients.<sup>103,104</sup> Several clinical data  
374 showed that 8-weeks treatment with montelukast prevents AR by

decreasing collagen deposition in airways in asthmatic children, and myofibroblast count in adults with mild atopic asthma.<sup>98,105</sup>

### Macrolides

Macrolides are antibiotics recognized for their anti-inflammatory properties, that can reduce exacerbation rate in SA.<sup>106</sup> Experimental data suggested that azithromycin administration decreases AECs apoptosis, attenuates goblet cell hyperplasia, suppresses EMT, reduces AHR, proliferation and viability of ASM cells.<sup>107–114</sup> Both roxithromycin and azithromycin inhibit vascular endothelial growth factor induced ASM cell proliferation in vitro.<sup>115,116</sup> A clinical trial showed that 8-months treatment with azithromycin (250 mg three days a week) increased LA in patients with SA on CT-scan without significant change of the WT versus placebo.<sup>117</sup>

### Biologics

Biologics, humanized antibodies used as add-on treatment in patients with SA, showed also benefits on AR.

In vitro administration of the anti-IgE antibody, omalizumab, prevented ASM cell proliferation, collagen and fibronectin deposition in allergic asthma.<sup>118,119</sup> Clinical data showed that 16-weeks treatment with omalizumab decreased airway WT on CT-scan in patients with SA.<sup>120,121</sup> Effectively, a significant reduction in RBM thickness and fibronectin accumulation was found on bronchial biopsies from patients with severe allergic asthma after 12-months treatment with omalizumab.<sup>122,123</sup> The decrease of fibronectin deposition in bronchial mucosa was associated with an improvement in asthma control and AQLQ.<sup>123</sup> Experimental and clinical studies demonstrated that omalizumab administration inhibited AHR in allergic asthma.<sup>124–126</sup>

Biologics targeting IL-5 (mepolizumab) and its receptor  $\alpha$  (benralizumab) showed positive impact on AR. One-year treatment with mepolizumab significantly decreased airway WA on CT-scan in patients with refractory eosinophilic asthma.<sup>127</sup> Mepolizumab reduced expression of ECM proteins (e.g. tenascin, lumican, procollagen III) and of TGF- $\beta$ 1 by eosinophils in bronchial biopsies from patients with mild atopic asthma, after 3-months of treatment.<sup>128</sup> Preliminary results from the MESILICO study showed that one-year treatment with mepolizumab significantly decreased RBM thickness, ASM area, and extent of epithelial damage in patients with late-onset, severe eosinophilic asthma and fixed airflow obstruction.<sup>129</sup> Benralizumab reduced the number of tissue myofibroblasts and ASM mass in bronchial biopsies from patients with severe eosinophilic asthma after 3-months of treatment.<sup>130</sup> Decrease in mucus plugs and ventilation defects were observed on functional imaging already at day 28 after benralizumab injection in patients with severe eosinophilic asthma, and the early response persisted 2.5-years later, alongside significantly improved asthma control.<sup>131–133</sup> Both mepolizumab and benralizumab suppressed the AHR induced by histamine in an experimental study, but this benefit was confirmed only for benralizumab in clinical setting.<sup>127,134–136</sup>

Experimental data showed that IL-4 receptor  $\alpha$  blockade by dupilumab decreased AHR, mucus production, and vascular permeability in the airways.<sup>137,138</sup> A prospective clinical study proved that 48-weeks treatment with dupilumab reduced mucus score and airway WT on CT-scan in patients with uncontrolled moderate-to-severe asthma. The decrease in mucus score was associated with improvement of asthma control, AQLQ, and airway obstruction.<sup>139</sup>

Tezepelumab, an anti-TSLP antibody, showed benefits on AR in a murine model of asthma by reducing collagen deposition, goblet cell hyperplasia, TGF- $\beta$  levels in the airways, and AHR to methacholine.<sup>140</sup> However, a recent randomized clinical trial failed

to prove a significant effect of tezepelumab after 28-weeks of treatment on AR assessed by bronchial biopsies, CT-scan and IOS in patients with moderate-to-severe asthma compared to placebo.<sup>141</sup> Other clinical data demonstrated a decrease of AHR to mannitol after at least 12-weeks of treatment by tezepelumab versus placebo, and a reduction of occlusive mucus plugs on CT-scan after 28-weeks of treatment.<sup>141–143</sup> The last effect was correlated with the improvement in FEV<sub>1</sub>.<sup>143</sup>

### Other Medications

Adding six standardized quality house dust mite sublingual immunotherapy to standard pharmacotherapy in patients with allergic asthma and rhinitis for 48-weeks significantly decreased airway WA and WT with increase in LA on CT-scan.<sup>144</sup> Fevipiprant, a prostaglandin D<sub>2</sub> type 2 receptor antagonist, administered 12-weeks reduced ASM mass on bronchial biopsies in asthma patients by decreasing airway eosinophilia with concomitant diminished recruitment of myofibroblasts and fibrocytes to the ASM bundle.<sup>145</sup> Increasing number of studies are focusing on potential therapies that could reduce ASM hypercontractility and AHR by improving abnormalities in calcium homeostasis and in airway innervation.<sup>24</sup> A clinical trial showed that gallopamil, a calcium channel blocker, administered for one year, reduces ASM area on bronchial biopsies and normalized ASM thickness on CT-scan.<sup>146</sup>

### Bronchial Thermoplasty

BT, an endoscopic treatment using radiofrequency energy, is the only therapy that lastingly decreased AR in 60% of adults with SA.<sup>1,147</sup> Besides the reduction in ASM mass, RBM thickening, submucosal nerves, and epithelium neuroendocrine cells, BT induces an ECM rearrangement with increase in tissue area occupied by collagen but a less dense fiber organization.<sup>147–151</sup> BT decreased AR by modifying the secretion of epithelium-derived heat shock proteins that improve AECs regeneration with negative impact on fibroblasts and ASM cells proliferation without affecting vasculature.<sup>147–149,152,153</sup> Histological parameters were associated with improvement of asthma control, AQLQ, lung function, and reduction of the exacerbation rate.<sup>151,154–156</sup> If the response to BT seems to be independent of the bronchodilator responsiveness, the patients with FEV<sub>1</sub> < 80% have a greater reduction in ASM mass after treatment compared to those with higher FEV<sub>1</sub>.<sup>156,157</sup> The reduction in ASM mass by BT becomes visible after 3-months of treatment and could persist > 10 years after the procedure.<sup>5,151,158</sup>

AR and chronic inflammation are critical components in asthma pathogenesis. Recognizing that AR may occur early in the disease and not simply as consequence of the inflammation is crucial to developing novel therapeutic strategies in asthma. AR is associated with a specific clinical phenotype of asthma. Understanding the complex mechanisms driving AR is mandatory to identify different pathological endotypes and for developing new therapies in asthma.

Advances in imaging techniques offer the possibility for an objective assessment of AR in the whole respiratory tract in asthmatics by broadly accessible, noninvasive, and highly reproducible tools. Imaging and lung function testing help clinicians to early detect and accurately evaluate the presence of AR in asthma patients.

Most of current therapies of asthma showed limited effects on AR because they are targeting inflammation and not ASM dysfunction. Even BT which acts directly on ASM mass showed benefits only in a selected population. Potential targets causing ASM cell dysfunction were identified, and medications are under study, but more efforts should be deployed on this research way to find effective treatments of AR in asthma.

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## Artificial Intelligence Involvement

None.

## Uncited Reference

36.

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