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Editorial ERJ: ERS/ATS Guidelines on Severe Asthma

Trustworthy Guidelines on Severe Asthma thanks to ERS and ATS

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Although severe asthma is estimated to be present in less than 10% of all asthmatics, these patients have the greatest morbidity and consume an overwhelming proportion of health care costs [1]. There have also been challenges defining the disease in terms of severity and control, characteristics which both lead to increased morbidity and mortality. Thus, the greatest unmet need in asthma care is in the severe asthma arena, where its heterogeneity with regard to clinical presentation and course has posed therapeutic challenges. The identification of clinical and molecular phenotypes, as discussed in this version of the severe asthma guidelines, move the field forward and will ultimately lead us to more personalized therapy. These guidelines describe the definition of severe asthma and provide recommendations for an approach to diagnostics and therapeutics given the data available today.

Clinical practice guidelines aim to help clinicians and healthcare professionals to make evidence-based decisions about the optimal care for patients [2]. In the past decade, the methodology and the science of developing guidelines have made major progress [3]. In contrast to narrative reviews or expert consensus-based clinical position statements (also called "strategic documents"), the development of guidelines requires that the evidence is appraised in a comprehensive and systematic manner and that the recommendations for practice are provided in a transparent manner [3,4]. The Institute of Medicine has published standards for trustworthy guidelines, providing recommendations on several crucial domains in the development process, including transparency, panel composition and conflict of interest [4-6]. Importantly, funders should not play a role in the development, and guideline panels should be multidisciplinary and include patients and/or patient advocates [6,7]. For the literature review and the grading of recommendations, a systematic approach is mandatory to rate the quality of the evidence, to summarize the benefits and harms of a given treatment, and to grade the strength of the recommendations [3]. Since ERS and ATS have adopted the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system for these methodological requirements, the ERS/ATS Task Force has succeeded in developing trustworthy, high-quality Guidelines on the Definition, Mechanisms, Evaluation and Treatment of Severe Asthma (see pages … in this issue of the ERJ) [8]. In addition, the ERS/ATS Guideline on Severe Asthma has many assets.

A first asset of the Severe Asthma Guidelines is a clear definition of severe asthma and uncontrolled asthma. When a diagnosis of asthma is confirmed and co-morbidities addressed, severe asthma is defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (long acting β2 agonist [LABA],

leukotriene modifier, theophylline or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy". The updated ERS/ATS Task Force definition thus focuses on severe asthma refractory to currently available medications using a simple definition that can be translated to clinical practice, in contrast to untreated severe asthma (as used previously in the first and second version of the Global Initiative for Asthma [GINA] guidelines) [9,10]. Uncontrolled asthma is defined by the presence of any one of four criteria, encompassing (1) poor symptom control, (2) frequent severe exacerbations, (3) serious exacerbations and (4) airflow limitation. This definition underlines the heterogeneity of uncontrolled severe asthma, since both patients with persistent airflow limitation and/or repetitive exacerbations qualify as uncontrolled asthmatics [11,12]. A similar classification approach has been used by the Global Initiative for Obstructive Lung disease (GOLD), since the updated strategic document qualifies COPD patients into the most severe category (GOLD category D) based on the presence of low lung function and/or frequent exacerbations [13].

A second asset of the ERS/ATS Guideline is the detailed chapter on the phenotyping of severe asthma, highlighting that severe asthma is a heterogeneous syndrome. Phenotyping integrates biological and clinical features and aims to improve therapy (by predicting the therapeutic response to available drugs in pre-specified phenotypes, or by identifying novel therapeutic targets in specific phenotypes) [14]. Important clinical features in phenotyping severe asthma are the age at onset of the disease, the presence or absence of allergy, the frequency of exacerbations and the level of airflow limitation [12,14,15]. An important biological feature is the nature of the underlying airway inflammation, discerning eosinophilic and non-eosinophilic (neutrophilic or paucigranulocytic) severe asthma [14,16]. While nitric oxide is currently not recommended to guide therapy in adults and children with severe asthma, it may be valuable to determine the inflammatory phenotype and decisions regarding the use of Th2 focused biologic therapy [17-19] . The crucial role of asthma phenotyping is well illustrated by the history of the clinical development of monoclonal antibodies against interleukin-5 (anti-IL5 mo abs; mepolizumab and reslizumab). In the original studies, anti-IL5 monoclonal antibodies were used as add-on therapy in patients with moderate-to-severe asthma, without phenotyping the underlying airway inflammation, and evaluating the effect on lung function as primary outcome [20,21]. These studies were negative. In contrast, when only patients with severe asthma and evidence of persistent eosinophilic airway inflammation were enrolled, add-on therapy with anti-IL5 monoclonal antibodies – on top of ICS and LABA - has been shown to reduce significantly the rate of moderate and severe exacerbations [22-24]. Similarly,

most RCTs of macrolide antibiotics did not show benefits in patients with moderate-to-severe asthma, explaining the sixth recommendation of the ERS/ATS Guideline [25-27]. However, a recent trial of long-term treatment with azithromycin in severe asthma suggests that patients with exacerbation-prone, non-eosinophilic asthma might benefit [28]. Although this hypothesis has to be confirmed in larger RCTs, the observations are in line with the proven efficacy of macrolides in other neutrophilic chronic airway diseases, including cystic fibrosis (CF), non-CF bronchiectasis and diffuse panbronchiolitis [29-32].

In addition to phenotype specific therapies, new therapies such as bronchial thermoplasty, have also been included for discussion and evaluation in this guideline. Bronchial thermoplasty is a unique, new therapy that employs radiofrequency heat applied directly to the airways as treatment for severe asthma [33]. There are data to suggest the effects are sustained but the asthmatic patients who received sham bronchoscopy were not followed long term [34]. The technique did reveal improvements in severe exacerbations, an outcome that is extremely important in severe asthma (AIR2 trial) [35]. However, until there are data that allow us to identify the best candidates for a procedure that is expensive and invasive, the recommendation for additional study and use in specialized centers put forth in this guideline is reasonable. There is considerable interest within the asthma community to study this therapy and hopefully add it to our armamentarium, as effective treatment of severe asthma is an unmet need. However, in an era of phenotype-driven therapy, bronchial thermoplasty should not be an exception.

Furthermore, the ERS/ATS Task Force has not only taken into account evidence on efficacy and safety of drugs in severe asthma from randomized controlled trials (RCTs), but also complementary evidence on real-life effectiveness, cost-effectiveness and long-term safety from observational studies. While classical RCTs provide the highest quality evidence, the outcomes reported from RCTs may not always be generalizable to real-world patients followed in clinical practice settings [36,37]. Indeed, classical RCTs, including tightly-controlled registration trials, investigate the effects of a new drug – compared with placebo - in specialized centers on surrogate outcomes (such as lung function) in highly selected patients, without co-morbidities but with optimal adherence to the study treatment and protocol. The ERS/ATS Workshop Report on Guideline Development as well as the respiratory effectiveness group (www.effectivenessevaluation.org) plead that guideline developers should also consider evidence from pragmatic trials and nonrandomized studies, investigating the real-life effectiveness and long-term safety of a treatment in large populations of heterogeneous patients followed in routine care [36]. Since real-world patients often have co-

morbid illnesses and low(er) adherence with medications, it is important to complement the efficacy data from RCTs – obtained in ideal circumstances - with effectiveness data from observational studies. The paucity of real-life effectiveness and cost-effectiveness data in severe asthma has contributed to the fact that the ERS/ATS Task Force has graded the quality of the evidence of most of the specific clinical recommendations on the treatment of severe asthma as "low" or "very low" and the strength of the respective recommendations as "conditional".

As the field of severe asthma is dynamic and not all areas are well supported by significant evidence in 2013, there are limitations to these guidelines. This is reflected in the relatively limited number of PICO (Patients/Intervention/Comparator/Outcome) questions which could be addressed by the ERS/ATS Task Force. This observation suggests that there must be updates to include the latest literature as the field moves forward to create a "living document". Examples of areas to expand upon in the future include the role of long acting muscarinic antagonists in severe asthma, the role of monoclonal antibodies targeting specific cytokines, how exhaled nitric oxide is best used in clinical practice and issues surrounding asthma pathobiology such as innate immune mechanisms, airway remodeling and the microbiome.

What we can do today is ensure that these guidelines are disseminated widely through our societies through thoughtful, coordinated action at our annual scientific meetings, but also through our journals, websites and other modes of communication such as webinars, podcasts and toolkits for providers and patients. We have a unique opportunity not only to disseminate, but implement these guidelines to ultimately improve the health of our patients with severe asthma.

References

1 Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 2007; 119:405-413

2 Schünemann H, Woodhead M, Anzueto A, et al. A guide to guidelines for professional societies and other developers of recommendations: introduction to integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society 2012; 9:215-218

3 Brozek JL, Akl EA, Jaeschke R, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. Allergy 2009; 64:1109-1116

4 Kuehn BM. IOm sets out "gold standard" practices for creating guidelines, systematic reviews. Jama 2011; 305:1846-1848

5 Kunz R, Fretheim A, Cluzeau Fo, et al. Guideline group composition and group processes: article 3 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society 2012; 9:229-233

6 Boyd E, Akl E, Baumann M, et al. Guideline funding and conflicts of interest: article 4 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society 2012; 9:234-242

7 Kelson M, Akl E, Bastian H, et al. Integrating values and consumer involvement in guidelines with the patient at the center: article 8 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society 2012; 9:262-268

8 Chung KF, Wenzel S, Brozek J, et al. International ERS/ATS Guidelines on Definition, Mechanisms, Evaluation and Treatment of Severe Asthma. Eur. Respir. J. 2014

9 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. NHLBI/WHO workshop report. National Institutes of Health, National Heart, Lung and Blood Institute;. National Institutes of Health publication no.95-3659. 1995

10 Global Initiative for Asthma. Global Strategy for asthma management and prevention. National Institutes of Health;. NIH publication no. 02-3659. 2002

11 Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet 2006; 368:804-813

12 Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 2010; 181:315-323

13 Vestbo J, Hurd SS, Agusti AG, et al. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, GOLD Executive Summary. American Journal of Respiratory and Critical Care Medicine 2012

14 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012; 18:716-725

15 Wenzel SE. Asthma: defining of the persistent adult phenotypes. The Lancet 2006; 368:804-813

16 Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178:218-224

17 Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab Treatment in Adults with Asthma. New England Journal of Medicine 2011; 365:1088-1098
18 Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. European Respiratory Journal 2013; 41:330-338
19 Corren J. Anti-interleukin-13 antibody therapy for asthma: one step closer. European Respiratory Journal 2013; 41:255-256
20 Leckie MJ, Khan J, O'Connor BJ, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. The Lancet 2000; 356:2144-2148
21 Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007; 176:1062-1071
22 Haldar P, Brightling C, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009; 360:973 - 984
23 Nair P, Pizzichini M, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009; 360:985 - 993
24 Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. The Lancet 2012; 380:651-659
25 Black P, Blasi F, Jenkins C, et al. Trial of Roxithromycin in Subjects with Asthma and Serological Evidence of Infection withChlamydia pneumoniae. American Journal of Respiratory and Critical Care Medicine 2001; 164:536-541
26 Richeldi L, Ferrara G, Fabbri LM, et al. Macrolides for chronic asthma. Cochrane Database Syst Rev 2005:CD002997
27 Cameron EJ, Chaudhuri R, Mair F, et al. Randomised controlled trial of azithromycin in smokers with asthma. European Respiratory Journal 2013; 42:1412-1415
28 Brusselle GG, VanderStichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013; 68:322-329
29 Equi A, Balfour-Lynn IM, Bush A, et al. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. The Lancet 2002; 360:978-984
30 Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non–cystic fibrosis bronchiectasis: The bat randomized controlled trial. Jama 2013; 309:1251-1259
31 Koyama H, Geddes DM. Erythromycin and diffuse panbronchiolitis. Thorax 1997; 52:915-918
32 Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. The Lancet 2012; 380:660-667
33 Wahidi MM, Kraft M. Bronchial Thermoplasty for Severe Asthma. American Journal of Respiratory and Critical Care Medicine 2012; 185:709-714
34 Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. Journal of Allergy and Clinical Immunology 2013; in press.
35 Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med 2010; 181:116-124
36 Wilt T, Guyatt G, Kunz R, et al. Deciding what type of evidence and outcomes to include in guidelines: article 5 in Integrating and coordinating efforts in COPD guideline

development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society 2012; 9:243-250
37 Avorn J. In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research. New England Journal of Medicine 2007; 357:2219-2221