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Approach to Patients with Severe Asthma: a Consensus Statement from the Respiratory Care Experts' Input Forum (RC-EIF), Iran

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ABSTRACT

Challenges in the assessment, diagnosis and management of severe, difficult-to-control asthma are increasingly regarded as clinical needs yet unmet. The assessments required to determine asthma severity, comorbidities and confounding factors, disease phenotypes and optimal treatment are among the controversial issues in the field.

The respiratory care experts' input forum (RC-EIF), comprised of an Iranian panel of experts, reviewed the definition, appraised the available guidelines and provided a consensus for evaluation and treatment of severe asthma in adults.

A systematic literature review followed by discussions during and after the forum, yielded the present consensus. The expert panel used the appraisal of guidelines for research and evaluation-II (AGREE-II) protocol to define an initial locally-adapted strategy for the management of severe asthma.

Severe asthma is considered a heterogeneous condition with various phenotypes. Issues such as assessment of difficult-to-control asthma, phenotyping, the use of blood and sputum eosinophil count, exhaled nitric oxide to guide therapy, the position of anti-IgE antibody, methotrexate, macrolide antibiotics, antifungal agents and bronchial thermoplasty as well as the use of established, recently-developed and evolving treatment approaches were discussed and unanimously agreed upon in the panel.

A systematic approach is required to ensure proper diagnosis, evaluate compliance, and to identify comorbidities and triggering factors in severe asthma. Phenotyping helps select optimized treatment. The treatment approach laid down by the Global Initiative for Asthma (GINA) needs to be followed, while the benefit of using biological therapies should be weighed against the cost and safety concerns.

Key words: Severe asthma, Definition, Comorbidities, Treatment, Phenotyping, Consensus statement, Iran

THE RESPIRATORY CARE EXPERTS' INPUT FORUM AND SEVERE ASTHMA

When a patient requires high intensity inhaled corticosteroids (HICS) and a long-acting beta-agonist (LABA) and/or systemic corticosteroids (CS) to prevent his/her asthma from becoming uncontrollable, or if the symptoms remain uncontrollable despite adequate therapy, the condition is referred to as severe, difficult-to-control asthma (1). According to the GINA, asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. Severe asthma requires step 4/5 (moderate- or high-dose ICS/LABA ± add-on); it may remain uncontrolled despite treatment (GINA 2014).

Despite notable advances in the diagnosis and treatment of asthma, its severe and refractory form still poses a clinical challenge (2). The recent international guidelines including the GINA (3) and ERS/ATS (European Respiratory Society and American Thoracic Society) (4) have laid down clinical recommendations for diagnostic and therapeutic approaches to severe asthma. However, these recommendations need to be customized for local implementation. Using the AGREE-II protocol (5), the Iranian panel of scientific experts in the field of pulmonary medicine came together in a Respiratory Care Experts' Input Forum (RC-EIF) to formulate a statement on the diagnosis and management of severe, difficult-to-control asthma.

This report is an overview of debates within the RC-EIF held in December 2014, in Iran. The present article provides a literature review on clinical issues in the diagnosis and management of severe asthma and a consensus on implementation of international guidelines in a local setting.

The aim of this RC-EIF report is to define clinical parameters of severe asthma, the phenotypes and recommendations for management of severe asthma based on available evidence, current international guidelines and input of experts involved in severe asthma management in adults. This report may also provide the basis for the development and implementation of locally-adapted guidelines on severe asthma management in the future.

INTRODUCTION

Around 6.5% of the Iranian population have asthma; the prevalence is increasing in major cities (6-11). Given the health burden of the disease, the national asthma and allergy strategy based on GINA and other international widely-referenced guidelines needs to be developed and implemented. The importance and necessity of having comprehensive national guideline for asthma should be further emphasized with certain criteria for referral. Beside the recently drafted and approved national guideline for asthma care addressing level-one and -two healthcare providers (general practitioners, family physicians and internists), a solid locally-adapted approach to subcategories of asthmatics and severe asthma patients needs to be defined.

Despite the fact that many asthmatic patients may be effectively controlled using the available medications, there is a subset of patients who remain refractory (12). These patients have considerable health expenditures (13, 14). There is much to be answered regarding the possible underlying mechanisms governing asthma unresponsive to treatment and the best approach to manage such patients. The definitions of severe/refractory asthma were agreed upon as variations of such patients had been adopted previously (15). Just recently, an American-European task force comprised of clinicians and scientists with special expertise in severe asthma was established to revisit previous definitions, define possible phenotypes of severe asthma, propose methods for its evaluation and provide recommendations on treatment (4). Severe asthma is regarded as a heterogeneous disease, with various phenotypes. The investigations suggested phenotypic biomarkers and targeted biologic therapies which partly succeeded to show efficacy (4).

MATERIALS AND METHODS

A. The expert panel composition and consensus

A panel of experts from pulmonary medicine and allied fields discussed the current evidence, limitations and clinical peculiarities in the management of severe and refractory asthma. Each participant was selected based on clinical expertise and academic records in the field of asthma. All experts interacted in contextual question-based round table discussions during this forum. A systematic approach toward key issues was taken including: 1) definition and clinical correlates of severe asthma, 2) assessment of comorbidities and contributory factors, 3) approaches to asthma phenotyping, and 4) treatment options. The available information together with expert opinions were compiled to draw a consensus.

Following a systematic literature search, documents featuring clinical perspectives of severe asthma and recommendations for the diagnosis and treatment were isolated for review and discussions. The most recent guidelines (3, 4) and related scientific publications were circulated among all RC-EIF attendees two months prior to the event.

After defining a list of contextual questions, a series of plenary talks and interactive round table discussion were conducted; the AGREE-II protocol was employed to appraise international guideline statements for local implementation. The AGREE-II protocol which can be applied to any set of guidelines in health care such as health promotion, public health, screening, diagnosis, treatment or interventions is perhaps regarded as one of the simplest methods of appraising and customizing international guidelines for locally-adapted strategies (5).

The section moderators of this EIF proposed several questions related to the definition and characteristics, diagnosis and treatment of severe asthma. These contextual questions (CQs) were defined two weeks prior to the meeting with key CQs on the diagnosis and treatment of severe asthma isolated and ranked by priority. Five CQs were selected to be explicitly discussed to provide clinical insight into optimal, evidence-based care in severe asthma.

The panel assessed the evidence in response to each CQ and appraised international guidelines on using the AGREE-II protocol. The expert panel further evaluated the outcomes of interest for each question in ameliorating the burden of severe asthma. The CQs assessed the research evidence and available international guidelines outlined below (Figure 1).

CQ1: With regard to asthma care, how can healthcare providers' adherence to guidelines affect healthcare outcomes?

CQ2: Based on the latest international guidelines (GINA, ERS/ATS), what are the knowledge and practice gaps for management of severe asthma in our setting?

CQ3: How are severe/refractory asthma comorbidities and contributory factors characterized and evaluated?

CQ4: Where should we place ICS, ICS/LABA and LTRAs and the newer therapies including monoclonal antibodies in the hierarchy of management of adults with severe/uncontrolled asthma?

CQ5: With regard to asthma care, how may adherence to guidelines by healthcare providers affect clinical outcomes?

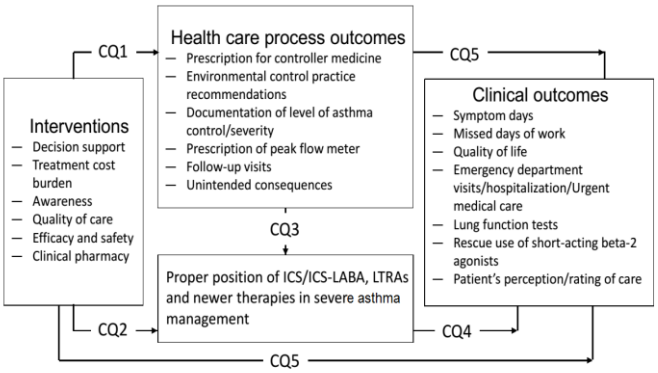

Figure 1. When addressing the five contextual questions (CQs) associated with the clinical decision in severe refractory asthma management, the outcomes of Interest for each question in ameliorating the burden of severe asthma were also discussed based on research evidence and available international guidelines on severe asthma. ICS: Inhaled corticosteroids, LABA: Long-acting beta-agonists, LTRAs: Leukotriene receptor antagonists.

B. Literature review

A systematic literature search in PubMed, MEDLINE, Scopus, Cochrane Central Register of Controlled Trials and Google Scholar databases (1990-2014) was done using a combination of keywords including severe asthma, refractory asthma, phenotyping, severe asthma management and recommendations. Following evaluations, documents featuring clinical perspectives of severe asthma and recommendations for the diagnosis and treatment approaches were isolated for review and discussion. When there were no randomized controlled trials (RCT) available with respect to the outcome of interest, the best available evidence to support or abrogate the clinical approach was considered. After the EIF, a systematic review was done to ensure all RCTs and related research was retrieved and assessed. The summary of evidence was reviewed and commented upon by the expert panel both during and after the meeting through face-to-face discussions and conference calls, respectively. The reviewed original documents were examined to judge available evidence.

The definition of severe asthma was discussed and agreed upon on the basis of previous (16) and more recent (17, 18) studies according to ATS/ERS' task force definition for asthma control and severity (4). With regard to asthma phenotyping, severe asthma evaluation and treatment approach, the relevant literature was reviewed and combined with the experts' views to arrive at a practical agreement or consensus.

RESULTS AND DISCUSSIONS

The literature review and experts' views obtained during our RC-EIF summarized the following: 1) Assessments needed to determine severe, difficult-to-control asthma, 2) Evaluation of comorbidities and confounding factors, 3) Early phenotyping as an essential step in optimized therapy, and 4) Current treatment approaches. The recommendations were made with data at hand and the basis of the AGREE-II protocol appraising international guidelines (GINA, ERS/ATS) in line with adopted strategies.

C. The assessments needed to determine severe, difficult-to-control asthma

i. Evidence review

Generally, patients with over six months of symptomatic air flow limitation , restriction of function, or chronic, incapacitating asthma and severe, acute exacerbations (in spite of continued medication) are considered to have severe asthma (12). However, according to the literature, up to 30% of non-asthmatic patients may falsely be diagnosed as severe, difficult-to-control asthma (19, 20). The initial assessments should entail careful history-taking regarding symptoms such as cough, wheezing, dyspnea (upon exercise), and nighttime awakenings. Additional information about the environmental or occupational factors and factors contributing to exacerbation should be obtained. Often, the obesity-related disordered-breathing is mistaken with asthma (21, 22).

In fact, individuals should be assessed for other conditions, which may mimic asthma or be associated with it. Assessment of reversible airflow limitation (including inspiratory and expiratory loop-spirometry, before and after bronchodilator use) should be performed as part of asthma diagnosis (23, 24). Medications may need to be withheld to better assess the reversibility of symptoms. In case of inconsistencies among history, physical findings and spirometry results, and when lung function is relatively preserved, confirmatory pulmonary function evaluations such as diffusing capacity, as well as bronchoprovocation with methacholine or exercise challenge test may be warranted (25, 26).

The routine use of chest high-resolution computed tomography (HRCT) scans in patients with suspected severe asthma based on history, presenting symptoms and/or results of other evaluations, is open to debate. Based on the experts' views in the present EIF, the use of chest HRCT should depend on the results of earlier tests

performed in the diagnostic pathway. For instance, in patients with suspected allergic bronchopulmonary aspergillosis, with a positive prick test to aspergillus antigen, chest HRCT would be clinically indicated (19, 27). Meanwhile, the question of whether chest HRCT is needed in patients with severe asthma or not (without other solid indications for that test) was discussed based on the evidence.

Having searched the literature, we could not locate any systematic review or longitudinal reports investigating the results of chest HRCT use to screen for masquerading or comorbid conditions in patients with severe asthma. We however retrieved some related observational studies the majority of which did not report on masquerading or comorbid conditions (27-30). Two of these observational reports were case series and revealed no data about the number of sampled patients (31). In one report, the comorbid/masquerading condition was diagnosed before HRCT was done (32) and in some other studies, HRCT was selectively done upon apparent indications other than the presumed severe/uncontrolled asthma (33-37).

Taken together, five reports provided inconsistent results of chest HRCT in severe asthma patients (38-42). In a report by Grenier et al, 30% of asthma cases who demonstrated no obvious change in serial chest radiography were found to have bronchiectasis on HRCT. However, only less than 15% of these patients fulfilled the criteria of severe asthma (38). Paganin et al. reported 13 and 37 patients with possible severe asthma and no specific selection criteria in two studies where the sampled population was undescribed (39, 40). In both reports, most patients were found to have either bronchiectasis or emphysema on HRCT. In a retrospective analysis by Jensen et al, 20% of severe asthma patients who had HRCT for unreported reasons demonstrated bronchiectasis (37). When the HRCT of severe asthma patients was compared with cases with bronchiolitis obliterans, the only more pronounced finding in patients with severe asthma was the mosaic pattern of attenuation. Bronchial dilatation was reported in 50% of severe asthmatic patients (43). In a recent report by Boulet et al, the HRCT in corticosteroid-naive mild stable asthmatic patients revealed no bronchiectasis while some patients showed emphysema-like changes (of which the majority were smokers) (43). A report by Takemura et al. demonstrated bronchial dilatation in few patients who had severe asthma according to GINA (41). Lastly, in a case series of 68 elderly subjects in whom asthma was unlikely to be severe (with an FEV_1 of 77% and 100% among early-onset and late-onset cases) (42) HRCT revealed emphysema and bronchial dilatation in 21% and 13% of early-onset asthma cases, respectively.

Our systematic literature search returned no studies indicating the prevalence of other masquerading or comorbid findings in severe asthma patients. Our search did not provide any report on the accuracy of chest HRCT in severe asthma. With reference to the international guidelines, neither GINA (3) nor other current guidelines (4) had made any recommendations regarding the position of chest HRCT in severe asthma.

ii. Experts' statement

1. Based on the reviewed evidence, our expert panel suggested that the use of chest HRCT should only be considered upon atypical presentation in patients suspected for severe asthma. Atypical presentations include excessive mucus production, lung function deterioration and diminished carbon monoxide transfer factor coefficient.
2. Careful history-taking and physical examination, spirometry of both inspiratory and expiratory loops pre- and post-bronchodilator usage and when indicated, complete pulmonary function tests including diffusing capacity should be considered as assessment measures in severe, difficult-to-control asthma. However, severe airflow limitation (FEV1<50% predicted or <1.0L) is a contraindication to bronchoprovocation with methacholine test (25).

D. Evaluating comorbidities and confounding factors

i. Evidence review

The common causes of admission of asthmatic patients to the intensive care units include the continued exposure to triggers or second-hand smoke (44, 45), incomplete assessment of comorbidities like sleep disordered breathing (SDB) including obstructive sleep apnea syndrome (OSAS) (46, 47), gastroesophageal reflux disease (GERD) (48, 49), or Aspirin-Exacerbated Respiratory Disease (AERD) (50) lack of adherence to medication (51, 52), inadequate follow-up (53) and varied response to medications (54). Severe, uncontrolled asthma is frequently associated with comorbidities and the lack of adherence to treatment should always be considered in such cases. Based on the evidence, lack of adherence may be seen in as many as 55% of severe asthma patients (19, 55, 56). Poor knowledge on proper use of inhalers is common among patients and needs to be carefully addressed (57). Methods measuring the compliance to ICS use are not widely applied in clinical practice. While pressure-actuated counters are only available on some new devices, canister weight is almost always a useful measure. On the other hand, the adherence to oral medications can be assessed through examining serum prednisolone, theophylline, systemic CS side effects and suppression of serum cortisol levels. Strict policies should be defined to ensure that patients get the prescriptions refilled only after their physicians' order (56). In the event of non-adherence, clinicians may plan to develop interventions to improve patients' level of adherence to therapy (53). The treatment cost per se may have a substantial effect on this (58).

While allergy and atopy have a solid association with asthma, large epidemiologic studies have shown that severe asthma is less linked with allergy as compared to mild to moderate asthma (59). Nevertheless, even in severe asthma, detection of any association between a specific IgE (revealed by skin prick or serum testing) through an ongoing exposure and the symptoms may help in identifying a contributory factor to asthma exacerbations (60).

Rhinosinusitis has been reported in a vast majority of asthmatic patients (61, 62). Meanwhile evidence for nasal polyps has been found in a fraction of asthmatics especially those with cystic fibrosis or primary ciliary dyskinesia (61, 63). The prevalence of NSAID sensitivity or AERD is <5%, however it may affect 20 to 40% of patients with asthma associated with chronic rhinosinusitis and nasal polyps (64).

While GERD is reported in almost 70% of asthma patients (48, 65, 66), anti-reflux treatments have resulted in moderate or no benefit in the control of asthma symptoms (67, 68). The term 'silent GERD' as an underlying contributor to poor asthma control may have been overestimated; however assessment for occult GERD and related treatments in case of confirmed diagnosis should always be considered (68). The symptoms arising from GERD and rhinosinusitis may not only hamper vocal cord function but also masquerade as asthma (69).

Obesity is another comorbidity linked with severe and difficult-to-control asthma. Its association with asthma may largely depend on the age at onset (70, 71).

Sadly, the worldwide health threat, smoking, has become more popular among youngsters in our community over the past decades (72-77). It can make asthma more difficult-to-control (78). The inflammatory processes seem to be altered in smokers leading to an attenuated response to CS (79, 80). Some reports have suggested testing the urinary and salivary cotinine in asthmatic patients as the test often reveals evidence of exposure to second-hand smoke (81-83). On the other hand, environmental factors such as ozone levels are directly linked with asthma outcomes in urban populations (84, 85). Given the critical importance of air pollution in our major cities, well-designed studies on environmental exposures and severe asthma are urgently required.

The prevalence of anxiety and depression in adults with severe asthma has reached 50% in some reports (47, 86-88). Such conditions are frequently subject to oversight. Therefore, when indicated, a proper psychiatric assessment and providing the required care is imperative (89). There

are no established psychological interventions to help behavioral aspects of asthma. A Cochrane meta-analysis has evaluated various relaxation and behavioral interventions in asthma patients showing moderate benefits in asthma outcome (90).

Lastly, when addressing asthma-related comorbidities, therapy-induced issues pertaining to the overuse of inhaled and systemic CS should also be considered (91-93).

ii. Experts' statement

1. Asthma is frequently linked with various comorbidities such as rhinosinusitis, GERD, OSAS, AERD, and psychopathologies. The environmental factors and lack of adherence to therapy may often give rise to difficult-to-control asthma. For many of these, how the conditions interact with asthma is yet to be further explained especially in case of severe asthma
2. . When relevant, comorbidities should be appropriately treated as they may affect the outcome.

E. Early phenotyping an essential step in optimized therapy

i. Evidence review

Severe asthma is unanimously recognized as a heterogeneous condition meaning that not all patients respond similarly to a given therapy or demonstrate a comparable clinical course. Asthma phenotyping does not follow a standard paradigm; hence no commonly-accepted definition of specific asthma phenotypes are available yet. Nonetheless, defining the specific characteristics of asthma phenotypes may not only help promote targeted therapies but also help define the expected course of the disease in some patients (94, 95). As such, studies have proposed some characteristics including eosinophilic inflammation, T helper-2 (Th2) processes and obesity as phenotype determinants. Such determinants can be helpful upon prescribing non-targeted (CS) or targeted (LTRA, anti-IgE, anti-IL5 and anti-IL13 antibody) therapies in asthmatics (71, 95-101).

The presence of neutrophilic inflammation in the sputum of patients with difficult-to-control asthma has been associated with diminished response to CS therapy (99). Although such measurements are available at referral centers in our country, their utility and methodology need to be standardized before suggesting wide usage.

Some studies with clinical inconsistencies both in the definition of asthma exacerbations and the cut-off level of eosinophils in the sputum enrolled a relatively low number of subjects and the examinations appeared to be insufficient (99, 102, 103). One study concluded a possible decrease in treatment costs of severe asthma in a single hospital setting once the treatment was guided via sputum eosinophils count (99). When attempting to characterize severe asthma and individualized care, a contextual issue is whether severe asthma treatment should be guided by sputum eosinophil count, rather than clinical criteria alone. Since the clinical advantage of sputum eosinophil-guided treatment vs. treatment guided by clinical criteria alone is uncertain, further evidence is required to suggest phenotyping in asthma patients based on sputum eosinophil count.

Other potential biomarkers for Th2 inflammation include exhaled nitric oxide (FeNO) and blood eosinophils (98, 104, 105). FeNO may not be elevated in younger patients with chronic asthma, and a low level is suggestive of conditions such as cystic fibrosis and ciliary dyskinesia (105, 106).

Except for blood eosinophils, other biomarker measurements in asthma need specialized equipment and assays, which are not readily available. Moreover, the utility of these biomarkers to identify clinically- and therapeutically-distinct phenotypes should be further examined (107, 108).

Bronchial thermoplasty (BT) is a recently validated method shown to improve control in severe persistent asthma. Some recent evidence supports the fact that BT reduces asthma-associated systemic markers of allergic inflammation including blood eosinophils (109). Patients with severe persistent asthma and particularly those of eosinophilic phenotype, who demonstrate continued symptoms despite the adequate use of inhaled

corticosteroids and long-acting β2-agonists, may benefit from BT (109, 110).

ii. Experts' statement

1. Severe asthma is regarded as a heterogeneous condition characterized by the need for aggressive treatment with high intensity inhaled corticosteroids in combination with LABA + add-on. The condition comprises various pathophysiological phenotypes for which the net definitions are not agreed upon. Such heterogeneity hinders the characterization of the disease and selection of appropriate treatment. Our improved understanding about the various phenotypes of severe/ difficult-to-control asthma and the biomarkers for each of these phenotypes may assist us in optimizing treatment for severe asthmatics .
2. The cost vs. utility of biomarker (blood/sputum eosinophilia and/or FeNO)-guided treatments should be better examined before recommending wide usage of these tests in routine asthma management.

F. The established, recently-developed and evolving treatment approaches for severe asthma

While the efficacy of traditional controller medications, such as long-acting beta-agonists, leukotriene receptor antagonists and theophylline is well-supported in the management of asthma (111-113), their clinical use has not been well-documented in severe, difficult-to-control asthma. In many instances, a mixed combination of these medications may be required (113). LABAs are recommended for use in combination with ICS only (114). When salmeterol and formoterol are used without steroids, they are shown to increase the risks of more severe attacks (114).

i. Evidence Review

1. Using established asthma medications

a. Corticosteroid insensitivity

As discussed earlier in this report, severe asthma involves CS insensitivity; hence, despite adequate CS therapy asthma control may remain poor. Therefore, although CS is the mainstay of treatment in mild to moderate asthma, alternative molecular-targeted therapies may be sought to ameliorate inflammation and enhance CS sensitivity in severe asthma (115). Patients with severe, difficult-to-treat asthma tend to become dependent, refractory or insensitive to corticosteroids (116). To maintain even a partial control of severe asthma symptoms, up to one-third of such patients would require oral CS in addition to ICS (66). Based on two reports, the intramuscular injection of high-dose triamcinolone, partly recovered asthma symptoms, diminished sputum eosinophils and improved FEV_1 (117, 118). These findings support a relative insensitivity to such a treatment rather than a full resistance.

Corticosteroid insensitivity is likely associated with various comorbidities including smoking (119), obesity (120), vitamin D deficiency (121, 122), and non-eosinophilic inflammation in adults (123).

While the eosinophilic phenotype with high IL-5 and IL-13 levels, tend to respond to ICS in mild to moderate asthma, eosinophilic inflammation remains persistent in some asthmatics despite adequate ICS or even systemic CS therapy (59, 124, 125). The non-eosinophilic phenotype comprises a larger subgroup of asthma patients (125). A clear understanding of possible mechanisms underlying CS insensitivity has led to the development of novel treatments including p38 mitogen-activated protein kinase (MAPK) inhibitors (126) and histone deacetylase-2 (HDAC-2) recruiters (127).

Some immunomodulatory and immunosuppressive agents including cyclosporine A, gold salts, intravenous immunoglobulin G and methotrexate have been widely studied for their steroid-sparing properties in severe asthma. Despite the evidence showing improved CS sensitivity with these agents, their clinical benefits do not outweigh potential side effects (128-131).

b. Inhaled and oral CS therapy

The threshold daily doses of ICSs are outlined in Table 1. These are higher than the usual doses required to

achieve maximal therapeutic effects in milder asthma. There is individual variation in dose-efficacy of ICS with evidence suggesting that greater ICS doses may show greater efficacy in severe asthma (132, 133). Together, there seem to be insufficient data to support higher doses (over 2000 mcg/day) of ICS and ultra-fine particle ICS in severe asthmatics.

To control severe asthma, physicians may need to even quadruple the dose of ICS in some cases (134). Quadrupling the dose is not often practical in severe asthma since the patients are already maintained on high ICS doses (134, 135). As a result, once standard therapies are found insufficient, OCS is added to help induce and maintain control in severe asthma. Meanwhile, it has remained unclear whether low-dose continuous OCS should be preferred over multiple bursts to control exacerbations.

In case of continuous use, clinicians should be well-versed about the potential untoward effects of systemic and inhaled corticosteroids including the increased risk of fractures, cataracts, an increased risk of adrenal suppression and growth retardation in children, respectively (136-139). The weight gain induced by chronic use of systemic CS may per se have a negative impact on asthma control (140, 141). As per the recent guidelines, when systemic CS are continuously used, prophylactic measures should be taken to prevent loss of bone density (142).

Table 1. The threshold daily dose of inhaled corticosteroids in picograms considered as high in adults. The presumed high doses are provided from the summary of product characteristics.

Inhaled corticosteroid	Threshold daily dose in pg. considered as high in adults
Beclomethasone dipropionate	>1000 (DPI) >500 (HFA MDI)
Budesonide	>800 (MDI or DPI)
Ciclesonide	>320 (HFA MDI)
Fluticasone propionate	>500 (HFA MDI or DPI)
Mometasone furoate	>400 (DPI)
Triamcinolone acetonide	>2000

DPI: Dry powder inhaler; HFA: Hydrofluoroalkanes; MDI: Metered-dose inhaler. Pg: picogram

c. Short- and long-acting beta-adrenergic bronchodilators

Patients with severe asthma frequently suffer from persistent airflow limitation despite adequate treatments (1, 4). In some patients with severe asthma, the incremental dose of ICS, together with a long-acting beta-agonist (LABA) provides a more favorable control than the use of ICS alone. As such, patients with refractory asthma may demonstrate at least a partial response and reach a more tolerable state, even though their composite asthma control indices (such as Asthma Control Questionnaire-7 or Asthma Control Test, ACQ-7/ACT, respectively) fall within uncontrolled levels (132, 143, 144).

In some patients known to have 'brittle' asthma (those of rapid onset asthma with vigorous exacerbations), subcutaneous administration of the beta-agonist, terbutaline, has been tried but no comparative advantage of this approach over the repeated inhaled beta-agonist has been documented (145).

It should be noted that continuous and high dose of beta-agonists can paradoxically result in lack of asthma control in mild to moderate patients. This becomes more evident when patients are continuously treated with high doses of short-acting beta-agonists (SABAs) or LABAs without ICS (146-148). Severe asthmatics are frequently prescribed with LABAs plus 'as-needed' SABAs. There has been an association between increased rate of mortality and the use of beta-agonists especially when these agents are used beyond the recommended limits (92, 146, 148).

In severe asthma, the dose and treatment duration of beta-agonist agents frequently exceed those recommended by guidelines and this makes it hard to comment on the presumably safe upper dose limit. Some case reports have indicated that a medically-supervised decrement in the dose of beta- agonists in some severe adult asthma patients who take excessive beta-agonists has led to an improved asthma control (149).

To prevent the overuse of beta-agonists in severe asthma patients, especially in those showing side effects including tremor and palpitations and to help control asthma exacerbations, the use of ipratropium bromide aerosols is a supported option (150, 151). Although less effective, it is considered safer than beta-agonists and can be used as-needed during the day. The routine use of nebulizers has not been supported owing to a relative inefficiency in drug delivery. On the other hand, the use of pressurized metered dose inhalers (pMDI) with a spacer is recommended in severe asthma and upon exacerbations (152).

d. Slow-release theophylline

In moderate asthma, symptom control can be achieved when theophylline is added to ICS (113). Theophylline (plus low dose ICS) has also been shown to enhance peak expiratory flow rates and lead to asthma control in smoking asthmatics, who demonstrated CS insensitivity (153). It is then plausible that theophylline improves CS insensitivity in some cases. Nevertheless, no such investigation has been done in adults with severe asthma.

e. Modifiers of the leukotriene pathway

The well-established anti-inflammatory activity of corticosteroids, does not extend to inflammation mediated through the leukotriene pathway in the airways of asthmatic patients (154). Leukotriene receptor antagonist (LTRAs) can further reduce inflammation and improve symptoms when added to ICS therapy. The addition of a LTRA to ICS has led to improved lung function in three studies, which recruited adults with moderate to severe asthma not taking LABAs. Two of these reports were from aspirin-sensitive asthmatics in which 35% were on systemic CSs (155-157). However, in a study on 72 adults with severe asthma who were receiving LABA and ICS, adding montelukast failed to improve clinical outcomes in a two-week follow up (158).

On the other hand, in CASIOPEA study, montelukast added to the usual dose of budesonide in patients with mild to moderate asthma, significantly improved asthma control, regardless of patients' ICS dose. The onset of action was faster (evident from day-1) in ICS + montelukast vs. ICS + placebo treatment arm (159). In IMPACT study, the combination of fluticasone and montelukast showed equal efficacy to the combination of fluticasone and salmeterol. Patients receiving salmeterol plus fluticasone had a significantly higher incidence of drug-related adverse events compared to patients receiving montelukast plus fluticasone (10.0% vs 6.3%; P=0.01). Patients receiving salmeterol plus fluticasone had a significantly higher incidence of serious adverse experiences (7.4% vs 4.6%; P=0.022) (160). Furthermore, add-on montelukast in patients with mild to moderate asthma, insufficiently-controlled with ICS or ICS+LABA in a six-month prospective open-label observational study (MONICA), improved both asthma control and asthma-related quality of life (161). Based on the subanalysis of MONICA study, add-on montelukast significantly improved asthma symptoms over 12 months in all patients in the study. Asthma control improved in all patient subgroups. In addition, comorbid allergic rhinitis, younger age, shorter duration of asthma and treatment with only ICS and not ICS+LABA, were found to be indicators of better control with add-on montelukast (162)

Compared to LABAs, montelukast is less effective when added to ICS therapy in preventing exacerbations in moderate-to-severe asthma (163). Meanwhile, our systematic search yielded some more recent reports indicating the positive role of montelukast in treating both severe and mild forms of asthma (164-166). Using lung function tests and HRCT imaging, one study showed that

add-on therapy with montelukast improves distal lung function reflected by air trapping (but not airway wall thickness) in moderate-to-severe asthma (165). Based on the recent practice guideline, LTRAs are suggested as phenotype-guided treatment in patients with AERD (GINA 2014). Further research is needed to address the role of montelukast in severe asthma and to see whether aspirin-sensitive asthma phenotype responds better to montelukast than other phenotypes.

f. Long-acting muscarinic antagonists

When moderate- to high-dose ICSs with or without LABAs fail to help severe asthma symptoms, the use of tiotropium bromide may improve lung function and lead to symptom control (167, 168). In patients receiving high-dose ICSs and LABAs, adding tiotropium bromide provided improvement in FEV_1 and diminished the as-needed use of short-acting beta2-adrenergics. The combination can also slightly decrease the risk of severe exacerbations (167, 169).

2. Specific approaches directed towards severe asthma

Until recently, research endeavors to investigate the optimized treatments for severe asthma were trivial. This landscape is however rapidly changing now. Several well-designed trials are ongoing to investigate the novel molecular-targeted therapies in the adult population suffering from severe asthma The evidence on safety profile of these new treatment options is however scant and continues to evolve (97, 98, 104, 170-176).

For the time being, omalizumab is the only biologic drug available in clinical practice (177-181). To overcome the shortcomings of this drug, more recent investigations have introduced new monoclonal antibodies possessing a higher avidity towards IgE (e.g. ligelizumab and lumiximab) (182, 183). Many biological drugs with various mechanisms of action are being developed and investigated today. As already mentioned, it is crucial to identify asthma phenotypes as it would significantly help in selecting the most appropriate drug for the individual patient (182). Based on the phenotypes, the eosinophilic asthma cases are expected to better respond to Th2 pathway modifiers. As such, the promising agents, which target cytokines of Th2 pattern including IL-2, IL-13 or IL-5 (daclizumab, mepolizumab and lebrikizumab, respectively), are expected to offer favorable control in asthmatic patients with hypereosinophilia (115, 182). A review of randomized data on new treatments in severe asthma has been outlined in Table 2.

ii. Experts' statement

The combination of ICS and one or two additional controllers including LABA, LTRAs or oral theophylline remains the mainstay pharmacotherapy for severe, difficult-to-control asthma. Tiotropium bromide is an effective add-on controller therapy to ICS in severe asthma. No empirical data has suggested the advantage of multiple combinations of the above alternative controllers in the management of severe asthma. Therefore, one should monitor clinical parameters to ensure the optimum combination of the controller medications. In case of properly obtained and maintained control, upon clinical discretion, the treatment regime can be stepped down to find the lowest effective dose.

1. Based on severe asthma phenotyping in adults, novel molecular-targeted therapies may provide clinical benefits both through symptom control and abrogating the underlying pathogenesis of the disease. The clinical advantages of such evolving therapies should be weighed against possible safety concerns.

Table 2. Evidence on new treatments in severe asthma from randomized, double-blind, placebo-controlled, parallel- armed studies. ACQ: asthma control questionnaire, AHR: airway hyper-responsiveness, AQLQ: asthma quality of life questionnaire, FeNO: level of nitric oxide in exhaled breath, FEV1: forced expiratory volume in 1 second, OCS: oral corticosteroids, PEFR: peak expiratory flow rate, SABA: short-acting beta-agonist, SEA: Severe Eosinophilic Asthma, TNFa: tumor necrosis factor-alfa, w: week.

Reference	Severity (n)	Treatment	Outcomes	Summary results
(183)	Severe, OCS-dependent SEA patients, Omalizumab-treated (n=45)	Mepolizumab in patients receiving maintenance OCS (5–35 mg/day) for ≥ 6 months.	Reductions in OCS use and exacerbation rate	Patients previously treated with Omalizumab had similar OCS reduction (OR=2.15 vs. 2.53) and exacerbation rate reduction (33% vs. 29%) to those with no prior history.
(175)	Severe, with ≥2 exacerbations in past year (n=621)	Mepolizumab (75, 250 or 750 mg infusions at 4w), anti-IL-5, 52w	Frequency of exacerbations	Reduced exacerbations by 39 to 52% in all doses. No effect on ACQ, AQLQ or FEV1.
(174)	Severe (n=34)	SCH527123, CXCR2 receptor antagonist, 4w	Altered sputum and neutrophil activation markers	Reduced blood and sputum neutrophils. Reduced mild exacerbations. No reduction in ACQ score.
(98)	Moderate-to-severe (n=291)	Lebrikizumab, anti-IL13 antibody, 24w	altered pre-bronchodilator FEV1	Improved FEV1 compared to placebo, with greatest changes in high levels of periostin or FeNO group (post hoc analyses). No change in ACQ5. Exacerbations were 60% lower in the treated arm.
(170)	Poorly- controlled on high-dose inhaled CS (n=53)	Reslimuzab, anti- IL-5, 12w	ACQ FEV1 Sputum eosinophils	Improved ACQ score. Reduced sputum eosinophils. Improved FEV1.
(171)	Moderate-to-severe (n=294)	AMG317, anti-IL- 4Ra antibody, blocks IL-4 and IL-13, 12w	ACQ scores, Frequency of exacerbations	No change in ACQ or exacerbations
(104)	Severe (n=61)	Mepolizumab, anti-IL5, 50w	Exacerbations Symptoms, FEV1, AQLQ, AHR, sputum and blood eosinophils	Reduced exacerbations. Improved AQLQ. Reduced eosinophils.
(97)	Severe (n=20)	Mepolizumab, anti-IL5, 50w	Frequency of exacerbations, reduction in oral steroid	Reduced exacerbations, eosinophils and OCS dose.
(176)	Severe (n=309)	Golimumab, anti-TNFa, 24w	FEV1, Exacerbations, AQLQ, PEFR	Unchanged FEV1. No reduction in exacerbations, AQLQ and PEFR. Notable adverse effects.
(172)	Severe, CS- dependent (n=44)	Masitinib (3, 4.5 and 6 mg/kg/day), c-kit and PDGFR tyrosine kinase inhibitor, 16w	Oral CS dose, FEV1, ACQ	No difference in OCS dose. ACQ improved, no difference in FEV1
(184)	Moderate-to- severe (n=115)	Daclizumab, IL- 2R antibody, 20w	Altered FEV1 (%) Frequency of exacerbations	Improved FEV1. Reduction in daytime asthma scores and the use of SABA. Prolonged time to severe exacerbations. Reduced blood eosinophils.
(173)	Severe (n=26)	SCH55700, anti- IL-5, 12w	Sputum and blood eosinophils, symptoms, FEV1	Reduced blood and sputum eosinophils. No other significant outcomes.

CONCLUDING REMARKS

a. The RC-EIF comprising experts in Iran held a problem-oriented clinical forum in December 2014 to discuss the evidence and draw and agree on a stance taken on severe asthma. The discussions and literature review revolved around: 1- The assessments needed to determine severe, difficult-to-control asthma, 2- Evaluating comorbidities and confounding factors, 3- Early phenotyping as an essential step in optimized therapy, and 4- Current treatment approaches. International guidelines were reviewed (based on the AGREE-II protocol appraising the international guidelines to define locally-adapted strategies) to reach a consensus.

b. Severe asthma which remains difficult-to-control despite administration of combination of high dose ICS and long-acting bronchodilators poses a significant clinical challenge and an important health care problem. Education and awareness about asthma management as well as adherence to international (locally-adapted) guidelines and statements of experts are expected to improve health-care process and clinical outcomes in the management of severe asthma.

c. Management of severe asthma needs a systematic approach to ensure a precise diagnosis, identify comorbidities and trigger factors and evaluate compliance. Severe asthma phenotyping is becoming an integral element of such a systematic approach as it would help optimizing treatments. The combination of ICS, LABA, LTRAs or oral theophylline is the current pharmacotherapy for severe, difficult-to-control asthma. Tiotropium bromide is a more recent effective add-on controller therapy to ICS. Severe refractory asthma often requires regular OCS use, thus the risk of steroid-related adverse events is almost always an issue. The use of immunomodulatory and biologic therapies as an alternative approach has been considered with a wide variation in efficacy and safety profiles across trials.

d. The expert panel of RC-EIF is determined to address other key issues with regard to the management of asthma in future discussion forums. The ultimate idea is to provide locally-adapted statements on various aspects of asthma care.

AUTHORS' CONTRIBUTIONS

Ansarin K., Attaran D., Jamaati H., and Masjedi M.R., equally contributed to session moderatorship, literature review and plenary talks as well as summary of recommendations (sorted alphabetically as first-order authors). At second order, Abtahi H., Alavi A., Aliyali M., Asnaashari A.M.H., Farid-Hosseini R., Ghayumi S.M.A., Ghobadi H., Ghotb A., Halvani A., Nemati A., Rahimi Rad M.H., Rahimian M., Sami R., Sohrabpour H., Tavana S., Torabi-Nami M. and Vahedi P. equally contributed to this consensus through inputs and critical reversion of the manuscript for important intellectual content (sorted alphabetically as second-order authors). Torabi-Nami M. drafted the manuscript. Torabi-Nami M. and Ghotb A. provided technical material support. All authors read and approved the final manuscript.

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COMPETING INTEREST

The present report outlined the communications and experts' opinions during the RC-EIF held on 14 December 2014, Iran. The authors declare no competing interest upon

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