International ERS/ATS Consensus Definition, Mechanisms, Evaluation, and Treatment of Severe Asthma

ONLINE-ONLY SUPPLEMENT 1

Background for Criteria for Uncontrolled Asthma

The criteria for "uncontrolled asthma" were chosen based on previously published information from asthma guidelines and severe asthma networks. A score on Asthma Control Questionnaire (ACQ) of more than 1.5 and Asthma Control Test (ACT) of less than 19 were chosen based on data that suggest this cut-off identifies patients less-than-optimally controlled, and which is in line with the definition of "not well controlled" by current National Asthma Education and Prevention Program (NAEPP) guidelines [1-4]. Thresholds for frequent severe or serious exacerbations (as defined by the ATS-ERS Task Force on Asthma Control and Severity) were identified in SARP where >50% of the severe asthmatics had frequent oral CS bursts and nearly 30% had been hospitalized in the previous year, but in which large percentages of subjects had one or the other, but not both [5, 6]. Data from the Severe Asthma Research Program (SARP) cluster analysis suggest that pre-bronchodilator FEV1 (% predicted) is a better indicator of future risk than post-bronchodilator [6]. For instance, in the Moore clusters, 2 of the 3 clusters in which most of the severe asthmatics were found, post-bronchodilator FEV1 was >80% predicted (i.e. normal). Despite this normalization of FEV1 post-bronchodilator, there was a high degree of either health care utilization, systemic corticosteroid use or symptoms. These subjects, indeed, had a pre-bronchodilator FEV1 <80% predicted and often – much less than 80% predicted. Thus, suggesting that future risk concerns only those asthmatics with post-bronchodilator FEV1 <80% predicted one might miss up to two thirds of those at higher risk. In addition, in some of the first longitudinal follow up data from SARP of systemic corticosteroids use, low pre-bronchodilator FEV1 was one of the strongest predictors of requirement for systemic corticosteroids both at baseline and at 3–4 years of follow-up. However, it is agreed that future risk associated with FEV1 % predicted is a continuum, with increasing risk associated with progressively lower FEV1 % predicted values [7].
FEV1 % predicted is the only physiologic measure currently incorporated in the definition of severe asthma, yet FEV1 % predicted is neither sensitive nor specific for the identification of severe asthma especially in children.

References

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Supplemental Table 1. Available tools in the evaluation of a patient with severe asthma and typical situations in which they have been used

Test	Purpose	Comment
Physiologic		
Lung volumes	diagnosis, assessment of severity/risk	In patient with unexplained dyspnea or with smoking exposure.
Diffusing capacity of the lung for carbon monoxide (DLCO)	diagnosis	In patient with smoking exposure and possibly in adult onset asthma.
Nonspecific bronchial bronchoprovocation (exercise, methacholine, mannitol, etc.)	diagnosis	In patient with normal or near normal lung function in order to exclude asthma
Nasal nitric oxide (NO), electron microscopy, ciliary motility and function, genetic testing	diagnosis	When primary ciliary dyskinesia (PCD) is suspected.
Cardiac evaluation, with or without cardiopulmonary exercise test/echocardiogram	diagnosis	When evaluating patient with dyspnea that is out of proportion to the abnormalities noted on lung function testing.
Laboratory		
Aspergillus specific IgE (consider other fungi)	diagnosis	When elevated IgE, central bronchiectasis or high blood eosinophils
Quantitative IgG, IgA and IgM	diagnosis	When evaluating for immunodeficiency in patient with recurrent infections, bronchiectasis.
Sweat chloride (if necessary, genetic testing and/or nasal potential difference)	diagnosis	In a setting of bronchiectasis or history suggestive of ciliary disorder (e.g. history of infertility, family history of CF)
Anti-neutrophil cytoplasmic antibodies (ANCA)	diagnosis	When considering Churg Strauss syndrome or vasculitis.
Endoscopy		
Fiberoptic bronchoscopy with endobronchial biopsy or thoracoscopic biopsy	diagnosis	To rule out other conditions and possibly for phenotyping
Radiologic		
Multidetector computed tomography (MDCT) of a chest	diagnosis	When suspecting non-asthma respiratory disorders, and in the case of an abnormal chest X-ray. The following radiographic findings may suggest alternative disorders: - Ground glass: HSP, RB-ILD (if smoker), drug abuse (e.g. cocaine) - Bronchiectasis: ABPA, CF, atypical Mycobacteria or other systemic immunodeficiency - Emphysema - Airway tumors, foreign body
Psychological		
Psychosocial/psychiatric evaluation	diagnosis, assessment of severity/risk	Indicated when evaluating difficult asthmatic in which psychosocial disorders may be primary

Supplemental Table 2. Available tests for addressing co-morbidities in severe asthma and typical situations in which they have been used

Test	Purpose	Comment
Peak expiratory flow (PEF) (twice daily, preferably using electronic device)	diagnosis, assessment of severity/risk	When assessing PEF variability as measure of asthma control or impact of environmental exposures on PEF (e.g. occupational asthma).
Urinary or salivary cotinine	assessment of co-morbidity	When evaluating smoking exposure in children and adults
Fiberoptic rhinoscopy/laryngoscopy	diagnosis	When evaluating upper airway for rhinosinusitis and vocal cord dysfunction.
Computed tomography scan of the paranasal sinuses	diagnosis	When evaluating for chronic sinusitis.
Psychosocial/psychiatric evaluation	diagnosis, assessment of severity/risk	When evaluating difficult asthmatic in which psychosocial disorders may be confounding and influencing compliance/adherence
Obtaining pharmacy prescribing records	assessment of co-morbidity	When evaluating compliance/adherence

Supplemental Table 3. Therapy-induced comorbidities

Therapy-induced comorbidities
Growth failure/retardation in children
Weight gain/obesity
Osteoporosis/osteopenia
Cataracts/glaucoma
Dermal thinning/ecchymoses
Psychiatric illness/psychosis
Gastroesophageal reflux
Diabetes/glucose intolerance
Hypertension
Myopathy
Obstructive sleep apnea
Avascular necrosis
Pneumonia
Fungal infection

Supplemental Table 4. Available tools for phenotyping and typical situations in which they have been used

Test	Purpose	Comment
Exhaled nitric oxide (NO)	diagnosis, assessment of severity/risk, to guide therapy	Maybe be Indicated when assessing asthma control or adherence to steroids
Induced sputum for sputum eostinophils	diagnosis, assessment of severity/risk, to guide therapy	
Presence of specific and total IgE	diagnosis, assessment of severity/risk, to guide therapy	
Aspirin or lysine aspirin challenge	diagnosis	In suspected aspirin sensitive asthma. Done in an appropriate center.
Lung function fluctuation monitoring	Assessment of severity/risk	