

Severe asthma in children and adolescents

The majority of children and adolescents with asthma achieve full or sufficient control under therapy with inhalant corticosteroids (ICS), in some cases requiring a combination with long-acting beta-agonists (LABA) and/or leukotriene receptor antagonists (LTRA) and/or long-acting muscarinic receptor antagonists (LAMA). Still, a minority (estimated less than 30% of our patients) remain symptomatic, show poor control under the treatment, and can be classed as “difficult asthma.” These patients present problems in all different aspects of the disease: they may show severe or chronic symptoms, may have a very high demand for therapeutic intervention (eg, high-dose ICS, oral corticosteroids (OCS)), and may suffer from severe or frequent exacerbations and asthma attacks and thus have severely impaired quality of life.¹ This broad range of problems suggests that severe asthma in children and adolescents is not a clearly defined entity, but rather a collection of problems and symptoms associated with the synonym of severe asthma. This problem is addressed by the current

definition of severe asthma according to the ERS.² In an even more global kind of definition of severe asthma, WHO includes patients that are currently not or not sufficiently treated or that remain not fully diagnosed.³

The first important task when confronted with a patient with “difficult asthma” therefore is to thoroughly differentiate between genuine severe asthma and difficult-to-treat asthma⁴ (Algorithm No. 1). The most important questions for this differentiation are the following: is it really asthma or does a different condition mimic similar problems and symptoms to those seen in asthma? Is asthma aggravated with comorbidities, such as allergic rhinitis or obesity (if yes, make sure to address these properly)? Is the patient treated according to the current guidelines, treated with the right drugs and combination of drugs? Is the patient adherent to the current treatment; is she/ he taking the drugs correctly? Only after answering all these questions, after the patient is educated for the kind and application

Treatment Algorithm for Severe Asthma (SA) in Children and Adolescents

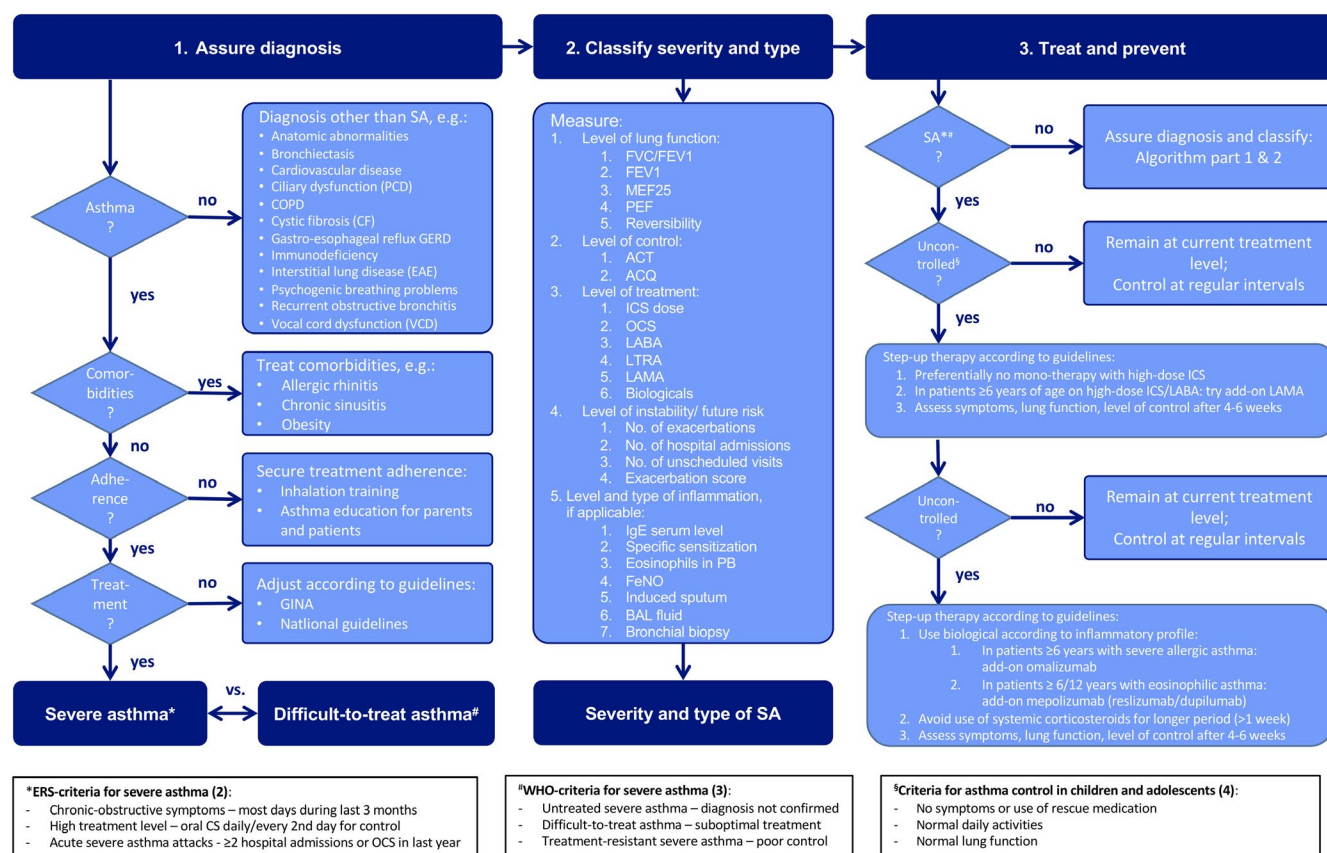


FIGURE 1 Priorities for treatment of severe asthma in childhood with biologicals. Priorities from 1 (highest/mandatory) to 4 (lowest) to justify treatment with biologicals

	slgE against perennial allergens	High total IgE serum levels	High FeNO levels	High numbers of eosinophils in PB
Consider anti-IgE	1	2	3	4
Consider anti-IL-5	4	3	2	1

modus of the specific treatment, and after any comorbidities are treated sufficiently, the diagnosis of genuine severe asthma can be conferred.⁴

After diagnosing severe asthma, the severity needs to be classified and the endotype of asthma should be characterized⁵ (Algorithm No. 2). For this purpose, the current lung function including reversibility, the level of asthma control, the level of current treatment, especially the use of systemic steroids, high-dose ICS, the regular or frequent use of SABA needs to be assessed. Next, the future risk needs to be addressed by assessing the number of exacerbations, hospital admissions and unscheduled visits in the past 12 month, since this provides the best forecast for future exacerbations. If possible, the subtype of inflammation of the individual patient should be characterized as good as possible by assessing the allergic status and type of specific sensitization (more than 80% of these patients will be allergic), numbers of eosinophils in the peripheral blood (eosinophilic airway inflammation with <90 cells/ μ L highly unlikely, with >400 cells/ μ L very likely), and FeNO (type-2 airway inflammation with FeNO < 20 ppb unlikely, with FeNO > 35 ppb likely)⁶ (Appendix S1). In children and adolescents who remain symptomatic under high-dose ISC or require systemic steroids, further investigations are warranted, for example by measuring airway inflammation by assessing induced sputum, BAL fluid or bronchial biopsies.⁷

When the diagnosis of severe asthma is established and the grade of severity and kind of inflammation is assessed, the patient should be stabilized (Algorithm No. 3). In symptomatic, not fully controlled patients, in many cases this can be achieved by stepping up from the current treatment, avoiding mono-therapy with high-dose ICS and rather adding a second or a third controller. In children ≥ 6 years of age, add-on LAMA is an option to stabilize the patient before the use of biologicals.⁴ In patients who—under a treatment of high-dose ICS plus a second or third controller—showed persistent poor symptom control over the last ≥ 3 months, required ≥ 2 systemic corticosteroid bursts, show impaired lung function, or were hospitalized due to asthma within the last 12 months, biologicals should be considered. In allergic asthma patients with specific sensitization against perennial allergens, high IgE and elevated FeNO levels, omalizumab is now very well established therapy with a high safety profile and considerable effectiveness in reducing exacerbations. New on the market, mepolizumab, a monoclonal antibody directed against interleukin 5 (IL-5) is a choice for children ≥ 6 (EU) or ≥ 12 years (US) of age with severe eosinophilic asthma and elevated numbers of peripheral eosinophils (Figure 1). Evidence for children and adolescents from the clinical trials with mepolizumab is limited and needs to be enlarged by future trials in this specific age group.⁸ Further biologicals against

IL-5 (reslizumab) or IL-4-receptor (dupilumab) will be available for the treatment of severe asthma patients under 18 years soon. It is important for the asthma specialist to oversee and assure responsible use of these expensive medications.⁹

One of the important issues in children and adolescents with severe asthma is to focus on the future risk. We know from longitudinal studies that declines in lung function in these patients are associated with a higher risk of chronic persistent asthma or COPD. Numbers of exacerbations in the last years are highly associated with the risk of future exacerbations. Therefore, close monitoring, regular follow-up investigations, and ongoing effort to improve symptom control and lower future risk are mandatory.

Eckard Hamelmann¹ 

Stanley J. Szeffler²

Susanne Lau³

¹Children's Center Bethel, Protestant Hospital Bethel, University of Bielefeld, Bielefeld, Germany

²Section of Pediatric Pulmonary and Sleep Medicine, Department of Pediatrics, Breathing Institute, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado

³Department of Pediatric Pneumology and Immunology, University Medicine Charité Berlin, Germany

Correspondence

Eckard Hamelmann, Children's Center Bethel, Grenzweg 10, D-33617 Bielefeld, Germany.

Email: Eckard.hamelmann@evkb.de

ORCID

Eckard Hamelmann  <https://orcid.org/0000-0002-2996-8248>

REFERENCES

1. Custovic A, Johnston SL, Pavord I, et al. EAACI position statement on asthma exacerbations and severe asthma. *Allergy*. 2013;68(12):1520-1531.
2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373.
3. Bousquet J, Mantzouranis E, Cruz AA, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol*. 2010;126(5):926-938.

4. *Pocket Guide for Diagnosis and Management of difficult-to-treat and severe asthma in adolescents and adult patients*. Global Initiative for Asthma; 2018.
5. Diamant Z, Vijverberg S, Alving K, et al. Towards clinically applicable biomarkers for asthma - an EAACI position paper. *Allergy*. 2019. <https://doi.org/10.1111/all.13806>
6. Del Giacco SR, Bakirtas A, Bel E, et al. Allergy in severe asthma. *Allergy*. 2017;72(2):207-220.
7. Bush A, Fleming L, Saglani S. Severe asthma in children. *Respirology*. 2017;22(5):886-897.
8. Szeffler SJ, Chipps B. Challenges in the treatment of asthma in children and adolescents. *Ann Allergy Asthma Immunol*. 2018;120(4):382-388.
9. Anderson WC, Szeffler SJ. Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: To biologic or not to biologic? *Ann Allergy Asthma Immunol*. 2019;122(4):367-372.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Date: 29-Mar-19

Manuscript Number: ALL-2019-00263

Title of Article: Severe asthma in children and adolescence

Name of the Corresponding Author: Eckard Hamelmann

Email Address of the Corresponding Author: Eckard.hamelmann@evkb.de

Appendix 1:

The role of eosinophils and FeNO for phenotyping of severe asthma in children and adolescents

Eosinophils: The term “eosinophilic” asthma (EA) generally refers to the clinical inflammatory phenotype of asthma wherein a significant number of sputum, airway, and/or blood eosinophils are present (1). Neither sputum nor BAL fluid nor bronchial biopsies are suitable components to measure eosinophilic inflammation in children with asthma. Therefore, numbers of eosinophils in peripheral blood may be used as a surrogate marker for this type of airway inflammation. The recommended range of peripheral blood eosinophilia considered consistent with EA has been derived from trials that target eosinophils in adult patients with severe asthma (2-4). Treatment with anti-IL-5 biologics was almost always successful in the range of 300 to 400 cells/ μ l, and studies with the anti-IL-5 antibody mepolizumab required only peripheral blood eosinophilia of 150 cells/ μ l or higher at screening, and 300 cells/ μ l in the preceding year to show efficacy (2,5). However, blood eosinophil counts do not necessarily reflect sputum eosinophil counts, and the two only correlate moderately with approximately 40% misclassification (6). Thus, very high or very low levels of blood eosinophils, respectively, may be a better approximation for predicting airway eosinophilia (7,8). Accordingly, adult patients with blood eosinophil counts less than 90 cells/ μ l were highly unlikely to have airway eosinophilia, but almost all patients with peripheral eosinophils higher than 400 cells/ μ l were likely to have EA (9). In children, valid data from trials are basically missing; therefore the data from the adult trials may be extrapolated.

FeNO: Nitric oxide (NO) in the respiratory system is produced mainly by two enzymes: constitutive nitric oxide synthase (NOS), which constantly generates low concentrations of NO, and inducible NOS (iNOS), which is expressed after stimulation by various inflammatory cytokines (10,11). Many studies found a correlation between FeNO and sputum eosinophilia, blood eosinophilia, serum eosinophil cationic protein, and IgE levels. FeNO therefore is considered a marker of a common asthma endotype characterized by Th2-mediated airway inflammation, eosinophilia, and responsiveness to inhaled steroids (12,13). In symptomatic children with asthma and a FeNO of less than 20 ppb, eosinophilic airway inflammation is unlikely. This cutpoint is based on a number of trials investigating the role of FeNO measurements to diagnose asthma and on studies designed to optimize ICS use. High FeNO of >35 ppb is likely to indicate significant airway eosinophilia, and that symptomatic patients will more likely show good responsiveness to inhaled steroids. (14). Persistent high FeNO in corticosteroid-treated symptomatic patients with asthma may reflect a specific endotype characterized by an increased risk of exacerbations (15).

In summary, symptomatic severe asthma in allergic patients with specific sensitization against perennial allergens, high IgE serum levels, high FeNO levels, with or without high eosinophils justifies a treatment attempt with anti-IgE antibodies;
 symptomatic severe asthma in patients with high numbers of peripheral eosinophils, high FeNO levels, with or without high IgE serum levels or specific sensitization justifies a treatment attempt with anti-IL-5 antibodies;
 in patients with symptomatic severe asthma with specific sensitization against perennial allergens, high IgE serum levels, high FeNO levels and elevated numbers of peripheral eosinophils, anti-IgE antibodies should be used for at least 3 months, hereafter in cases of poor response a treatment attempt with anti-IL-5 antibodies is warranted (Fig. 1).

1. [Carr TF¹](#), [Zeki AA²](#), [Kraft M¹](#). Eosinophilic and Noneosinophilic Asthma. [Am J Respir Crit Care Med](#). 2018 Jan 1;197(1):22-37. doi: 10.1164/rccm.201611-2232PP.
2. [Bel EH¹](#), [Wenzel SE](#), [Thompson PJ](#), [Prazma CM](#), [Keene ON](#), [Yancey SW](#), [Ortega HG](#), [Pavord ID](#); [SIRIUS Investigators](#). Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. [N Engl J Med](#). 2014 Sep 25;371(13):1189-97. doi: 10.1056/NEJMoa1403291. Epub 2014 Sep 8.
3. [Ortega HG¹](#), [Liu MC](#), [Pavord ID](#), [Brusselle GG](#), [FitzGerald JM](#), [Chetta A](#), [Humbert M](#), [Katz LE](#), [Keene ON](#), [Yancey SW](#), [Chanez P](#); [MENSA Investigators](#). Mepolizumab treatment in patients with severe eosinophilic asthma. [N Engl J Med](#). 2014 Sep 25;371(13):1198-207. doi: 10.1056/NEJMoa1403290. Epub 2014 Sep 8.
4. [Bleecker ER¹](#), [FitzGerald JM²](#), [Chanez P³](#), [Papi A⁴](#), [Weinstein SF⁵](#), [Barker P⁶](#), [Sproule S⁶](#), [Gilmartin G⁷](#), [Aurivillius M⁸](#), [Werkström V⁸](#), [Goldman M⁶](#); [SIROCCO study investigators](#). Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. [Lancet](#). 2016 Oct 29;388(10056):2115-2127. doi: 10.1016/S0140-6736(16)31324-1. Epub 2016 Sep 5.
5. [Bel EH¹](#), [Wenzel SE](#), [Thompson PJ](#), [Prazma CM](#), [Keene ON](#), [Yancey SW](#), [Ortega HG](#), [Pavord ID](#); [SIRIUS Investigators](#). Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. [N Engl J Med](#). 2014 Sep 25;371(13):1189-97. doi: 10.1056/NEJMoa1403291. Epub 2014 Sep 8.
6. [Hastie AT¹](#), [Moore WC](#), [Li H](#), [Rector BM](#), [Ortega VE](#), [Pascual RM](#), [Peters SP](#), [Meyers DA](#), [Bleecker ER](#); [National Heart, Lung, and Blood Institute's Severe Asthma Research Program](#). Biomarker surrogates do not accurately predict sputum eosinophil and neutrophil percentages in asthmatic subjects. [J Allergy Clin Immunol](#). 2013 Jul;132(1):72-80. doi: 10.1016/j.jaci.2013.03.044. Epub 2013 May 21.
7. [Wagener AH¹](#), [de Nijs SB¹](#), [Lutter R²](#), [Sousa AR³](#), [Weersink EJ¹](#), [Bel EH¹](#), [Sterk PJ¹](#). External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. [Thorax](#). 2015 Feb;70(2):115-20. doi: 10.1136/thoraxjnl-2014-205634 . Epub 2014 Nov 24.
8. [Zhang XY¹](#), [Simpson JL](#), [Powell H](#), [Yang IA](#), [Upham JW](#), [Reynolds PN](#), [Hodge S](#), [James AL](#), [Jenkins C](#), [Peters MJ](#), [Lin JT](#), [Gibson PG](#). Full blood count parameters for the detection of asthma inflammatory phenotypes. [Clin Exp Allergy](#). 2014 Sep;44(9):1137-45. doi: 10.1111/cea.12345.

9. [Westerhof GA](#), [Korevaar DA](#)², [Amelink M](#)³, [de Nijs SB](#)³, [de Groot JC](#)⁴, [Wang J](#)², [Weersink EJ](#)³, [ten Brinke A](#)⁴, [Bossuyt PM](#)², [Bel EH](#)³. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. [Eur Respir J](#). 2015 Sep;46(3):688-96. doi: 10.1183/09031936.00012415. Epub 2015 Jun 25.
10. [Turner S](#). Exhaled nitric oxide and the management of childhood asthma--yet another promising biomarker "has been" or a misunderstood gem. [Paediatr Respir Rev](#). 2015 Mar;16(2):88-96. doi: 10.1016/j.prrv.2014.07.005. Epub 2014 Aug 7.
11. [Kim HB](#)¹, [Eckel SP](#)², [Kim JH](#)^{3,4}, [Gilliland FD](#)⁵. Exhaled NO: Determinants and Clinical Application in Children With Allergic Airway Disease. [Allergy Asthma Immunol Res](#). 2016 Jan;8(1):12-21. doi: 10.4168/aaair.2016.8.1.12. Epub 2015 Jul 2.
12. [Borland C](#)¹, [Cox Y](#), [Higenbottam T](#). Measurement of exhaled nitric oxide in man. [Thorax](#). 1993 Nov;48(11):1160-2.
13. [Mahr TA](#)¹, [Malka J](#), [Spahn JD](#). Inflammometry in pediatric asthma: a review of fractional exhaled nitric oxide in clinical practice. [Allergy Asthma Proc](#). 2013 May-Jun;34(3):210-9.
14. [Dweik RA](#), [Boggs PB](#), [Erzurum SC](#), [Irvin CG](#), [Leigh MW](#), [Lundberg JO](#), [Olin AC](#), [Plummer AL](#), [Taylor DR](#); [American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels \(FENO\) for Clinical Applications](#). An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. [Am J Respir Crit Care Med](#). 2011 Sep 1;184(5):602-15. doi: 10.1164/rccm.9120-11ST.
15. [Dweik RA](#)¹, [Sorkness RL](#), [Wenzel S](#), [Hammel J](#), [Curran-Everett D](#), [Comhair SA](#), [Bleecker E](#), [Busse W](#), [Calhoun WJ](#), [Castro M](#), [Chung KF](#), [Israel E](#), [Jarjour N](#), [Moore W](#), [Peters S](#), [Teague G](#), [Gaston B](#), [Erzurum SC](#); [National Heart, Lung, and Blood Institute Severe Asthma Research Program](#). Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. [Am J Respir Crit Care Med](#). 2010 May 15;181(10):1033-41. doi: 10.1164/rccm.200905-0695OC. Epub 2010 Feb 4.

