

Guidelines

Severe Asthma in Children and Adolescents: an AWMF Guideline by the German Society for Pediatric Pulmonology

Schweres Asthma bei Kindern und Jugendlichen Zusammenfassung der AWMF-Leitlinie koordiniert von der Gesellschaft für Pädiatrische Pneumologie (GPP)

Eckard Hamelmann^{1,2}, Christina Schorlemer³, Nico Derichs⁴, Ernst Eber⁵, Michael Gerstlauer⁶, Andreas Jung⁷, Michael Kabesch⁸, Matthias Volkmar Kopp⁹ , Susanne Lau¹⁰, Christiane Lex¹¹, Alex Möller¹², Bianca Schaub¹³, Nicolaus Schwerk¹⁴, Thomas Spindler¹⁵, Christian Taube¹⁶, Christian Vogelberg¹⁷, Angela Zacharasiewicz¹⁸, Stefan Zielen¹⁹, Antje Schuster²⁰, Monika Gappa²¹

Affiliation addresses are listed at the end of the article.

ABSTRACT

Background Asthma is the most common chronic respiratory disease in children and adolescents. While most patients achieve good control with guideline-based treatment, a significant proportion experience persistent symptoms, frequent exacerbations, and impaired quality of life.

Objectives This guideline aims to define severe and difficult-to-treat asthma in children and adolescents, support diagnostic precision, and provide practical, evidence-based recommendations for assessment and management, including biological therapies.

Materials and methods The S1 guideline was developed under the coordination of the German Society for Pediatric Pulmonology following AWMF procedures. A structured consensus process involving experts from pediatric pulmonology, allergology, and general pediatrics was conducted. Existing national and international guidelines and new evidence were systematically reviewed and adapted.

Results Key elements include a stepwise diagnostic algorithm to distinguish difficult-to-treat from truly severe asthma, guidance on assessing adherence, comorbidities, and inflammation biomarkers, and recommendations for targeted biological treatment. This guideline addresses monitoring tools, transition to adult care, and the role of rehabilitation.

Conclusions Children and adolescents with severe asthma require early referral to specialized centers and a structured, interdisciplinary approach. Personalized treatment strategies—including biologics—should be guided by phenotyping and biomarkers. Registry data are essential to improve care quality and generate real-world evidence.

Keywords Paediatric asthma, severe asthma, biologicals, asthma management, practice guidelines

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Correspondence Prof. Eckard Hamelmann, Bethel Children Center – Department of Pediatrics, Protestant Hospital Bethel, Bielefeld, Germany, Email: Eckard.Hamelmann@evkb.de

Objective of the guideline (introduction to the topic)

This S1 guideline on severe and difficult-to-treat asthma in children and adolescents was commissioned by the German/ Austrian/ Swiss (DACH) Society for Paediatric Pneumology (GPP). The aims are to structure the diagnosis, classification and treatment of complex forms of asthma and to improve management in an evidence-based and practical manner. The recommendations are aimed at specialists in paediatrics and pulmonology as well as other professional groups involved in the management of children and adolescents living with severe asthma.

Introduction and definition

Asthma is the most common chronic respiratory disease in children. Symptoms include shortness of breath, wheezing, and coughing which vary over time; allergens, infections, exercise or weather may trigger exacerbations. Management of people living with asthma aims to achieve control, which means no symptoms, normal lung function and no exacerbations. Most patients achieve good symptom control, but a small proportion remains uncontrolled despite high levels of inhaled (inhaled corticosteroids [ICS]) or systemic steroid (oral corticosteroids [OCS]) treatment or biologics—this is where difficult or severe asthma begins.

The guideline classifies severity levels according to WHO (untreated, difficult, and refractory), ERS/ATS 2014 (permanently high ICS + second controller/OCS), GINA 2021 (uncontrolled under high ICS-LABA), National Disease Management Guideline (NVL 2024; long-term: > 6 mo) high dose ICS and/or add-on therapy with a long-acting anticholinergic (LAMA). The common features including adherence, technique, triggers and comorbidities must be carefully checked and optimized before classification.^{1–5}

Recommendation 1: Difficult asthma is defined as asthma in children and adolescents if there is no good symptom control and/or persistent impairment of lung functions on treatment level 4 (NVL) for > 6 months or if exacerbations ($\geq 1/y$) occur at this level of treatment. **Recommendation 2:** Optimize all modifiable factors first. **Recommendation 3:** If control improves after optimizing modifiable factors, the diagnosis is difficult-to-treat asthma. **Recommendation 4:** Severe asthma is diagnosed and despite optimization > 6 months high ICS + LAMA or biologics (level 5/6) is necessary.

This differentiation clearly separates treatment-dependent difficult asthma from treatment-refractory severe asthma and provides the basis for further management (**Fig. 1**).

Epidemiology in Germany, Austria and Switzerland

It is estimated that the prevalence of severe asthma in childhood in the DACH region is 0.2–0.5 %. Reliable, comparable data are still lacking. The German Asthma Net (GAN) register documents 163 children with severe asthma, corresponding to around 8 % of the asthma patients registered there.⁶

In Austria, the only available data come from the ISAAC study from 1998, where around 7 % of children with asthma were classi-

fied as having severe asthma. For Switzerland, U-BIOPRED provides individual data, but no reliable epidemiological statements.^{7,8}

Recommendation 5: Children and adolescents with severe asthma should be recruited in appropriate registries for severe asthma (e.g., in GAN) in order to improve evidence regarding epidemiology and real-life management.

Systematic, uniform recording is a central prerequisite for health services research and evidence-based health planning in the DACH region.

Management of difficult and severe asthma

Adherence

Lack of adherence to therapy is one of the most common causes of poor asthma control and should be ruled out before any treatment escalation of medical treatment. It is not only the frequency of use that is crucial, but also the correct inhalation technique. Digital tools for objective monitoring are helpful, but diaries alone are often unreliable. A therapeutic alliance between family and practitioners is key—understanding of the disease, treatment goals and joint decisions to strengthen motivation.⁹

Recommendation 6: To improve treatment adherence, a therapeutic alliance should be established between patients/families and health care professionals. **Recommendation 7:** Adherence, including an inhalation technique, should be checked at every visit. **Recommendation 8:** The agreed treatment plan should be documented in writing and handed out with instructions on the technique. **Recommendation 9:** Patients/families should be offered asthma education. **Recommendation 10:** If necessary, a qualified rehabilitation program should be offered.

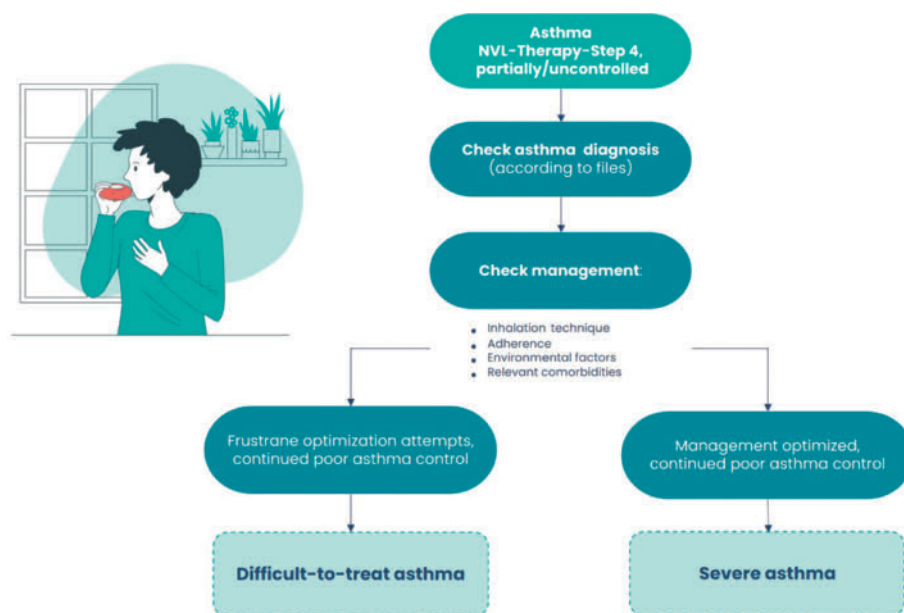


Fig. 1 Distinguishing between difficult-to-treat and severe asthma [rerif].

Confirming the diagnosis and ruling out differential diagnoses

Before a diagnosis of severe asthma can be made, it must be ensured that bronchial asthma is actually present.¹⁰ Repeated clinical and functional assessment in accordance with the recommendations of the S2k and NVL guidelines^{1,2} is essential. In the event of an unusual history (e.g., early onset, lack of response, and atypical findings), differential diagnosis of imitating or comorbid diseases must be considered.⁴ These include ciliary dyskinesia, chronic infections, tumours or congenital malformations (Tables 1 and 2).

Diagnostics may include a structured medical history, lung function testing, FeNO measurement and, if necessary, high-resolution computed tomography (CT), magnetic resonance imaging (MRI), bronchoscopy with bronchoalveolar lavage (BAL) and microbiological work-up. The involvement of a specialized centre is recommended^{11–13} (Fig. 2).

Recommendation 11: If severe asthma is suspected, the diagnosis of asthma should be reviewed and, if necessary, confirmed again. Recommendation 12: The recommendations of the current guidelines (S2k, NDMG) should be implemented. Recommendation 13: The diagnosis should be confirmed by a paediatric pulmonologist.

Table 1 (extract from original in guideline) Important differential diagnoses of asthma in children

Indications	Possible diagnoses
Symptoms since birth and peripartum abnormalities	BPD, CF, PCD, and chILD
Acute onset	Foreign body aspiration and malformations
Non-reversible obstruction and atypical clinic	Tumor, bronchiolitis obliterans, and ILO
Additional signs (clubbed nails and failure to thrive)	chILD, CF, and ciliary dyskinesia
Unilateral auscultation findings	Malformations and post-infectious lesions

Table 2 (extract from original in guideline) More common diffuse lung diseases as a differential diagnosis

Diagnosis	Symptoms	Diagnosis
CF	chronic cough, pneumonia, and failure to thrive	Schweißtest and Genetik
PCD	chronic cough and situs inversus	Nasal brush biopsy
chILD	Shortness of breath and restrictive lung function	CT and BAL
GER	Hoarseness and nocturnal cough	pH-metry
Tumor	Dyspnea and radiological mass	Imaging and biopsy if necessary

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography.

Recommendation 14: Special examinations (e.g., CT and bronchoscopy) should be considered and performed if necessary.

Recognizing and treating comorbidities

Many children with severe asthma also suffer from comorbidities (“asthma plus”) such as allergic rhinitis, atopic dermatitis or food allergies. Gastro-oesophageal reflux, obesity, nasal polyps, sinusitis, sleep apnoea or psychological stress (e.g., anxiety disorders) may also be present. These concomitant diseases influence the course of the disease, make management more difficult and should be actively identified and treated (Table 3).

Recommendation 15: If difficult asthma is diagnosed, a structured assessment of possible comorbidities should be carried out before treatment is intensified (including the possible introduction of biological therapy).^{14–17}

Monitoring for severe asthma

Structured monitoring is essential in managing children with severe or difficult-to-treat asthma. It enables effective treatment evaluation, early detection of exacerbations, and objective assessment of disease progression.

Key aspects of monitoring include symptom assessment, capturing exacerbations, lung function measurement, assessment of inflammatory markers, treatment adherence, quality of life, growth, and psychosocial stress. Assessments should be conducted regularly, with shorter intervals recommended during periods of disease instability.¹⁸

Symptoms and exacerbations should ideally be documented using validated scoring tools such as the (c)ACT, ACQ, or the exacerbation clinical score (ECS). The ECS enables a structured assessment of exacerbation risk and supports objective treatment decisions; however, a validation for children is still missing.¹⁸

Lung function (particularly FEV₁, and if indicated, FVC and RV/TLC) is routinely assessed using spirometry and, when necessary, body plethysmography. In the case of severe asthma, a persistently reduced FEV₁ < 80 % may indicate an increased risk of long-term complications.^{19,20}

Inflammatory activity is monitored via FeNO (serial measurements recommended) and blood eosinophils. The determination of eosinophils in the differential blood count and the measurement of FeNO as biomarkers have been shown to be useful for monitoring inflammation and changes during therapy.^{21–28}

Quality of life and psychosocial aspects (e.g., school absences and family stress) should be recorded at least once a year. The PAQLQ is a validated instrument for children aged 8 years and older.^{29,30}

Growth must be documented every 6 months (height, weight, BMI, and percentile progression) in order to detect side effects of inhaled or oral steroids at an early stage.

Recommendation 16: Symptoms, exacerbations and lung function should be recorded every 3 months. Recommendation 17: FeNO should be measured repeatedly to monitor inflammation. Recommendation 18: Quality of life should be assessed annually using validated questionnaires. Recommendation 19: Height and weight should be measured regularly and documented on a percentile basis.

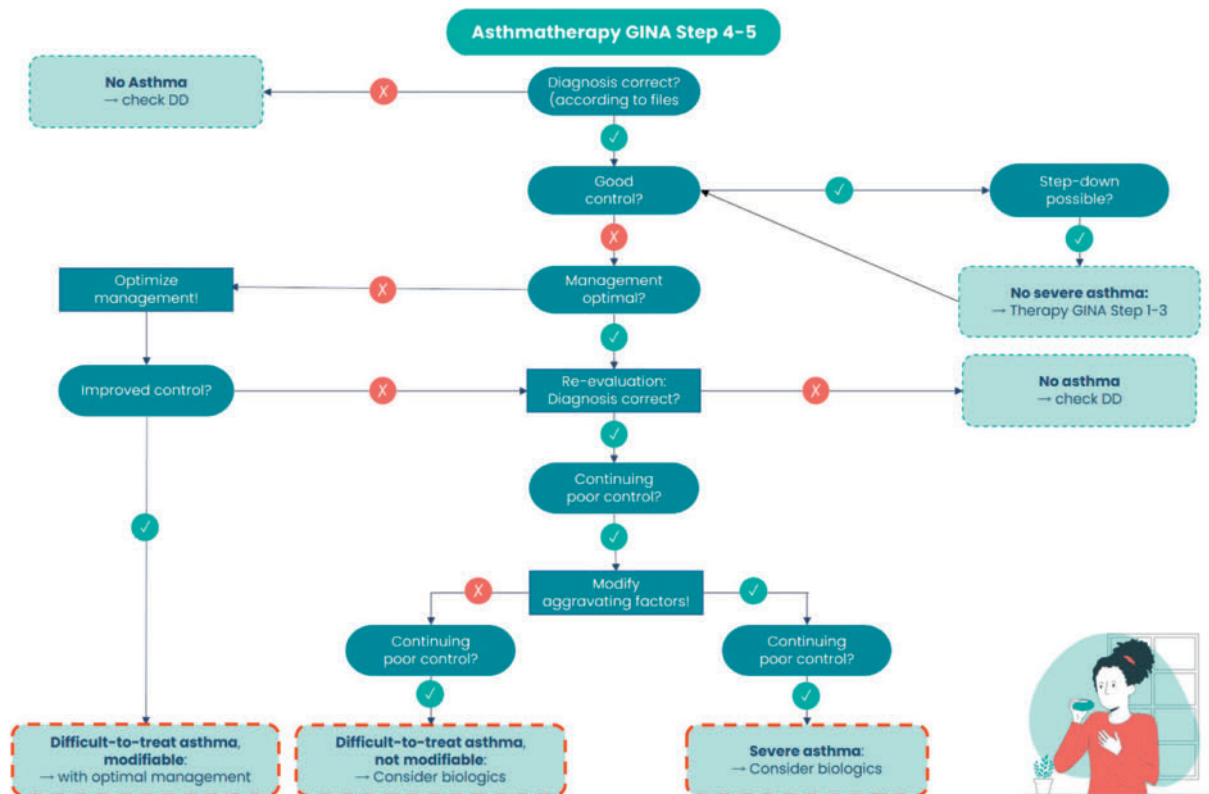


Fig. 2 Assessment and treatment decisions for difficult-to-treat and severe asthma [rerif].

Drug therapy

Initial therapy und step-up therapy

The goal of long-term asthma management is to achieve an optimal symptom control using the lowest effective dose of medication ("as much as necessary, as little as possible") and reduce future risks. The basis is the step-by-step escalation according to the NVL/S2k guideline.

Step 4 involves a combination of medium-dose ICS with LABA, preferably as a fixed-dose combination. This regimen may be supplemented with LTRA or LAMA, if needed. The SMART approach (using ICS/formoterol as both maintenance and reliever therapy) is also approved for adolescents (> 12 years of age).

Stage 5 includes high-dose ICS in combination with LABA and possibly LAMA/LTRA. Due to possible systemic side effects, close monitoring and a time limit are necessary here.

Recommendation 20: OCS should only be used in the short term (max. 1 week). Recommendation 21: If long-term therapy with ICS at a medium daily dose + LABA fails, LAMA should be used in addition. Recommendation 22: High-dose ICS should be closely monitored and used for a limited time.

Choosing and using biologics correctly

For children and adolescents with severe asthma, biologics are the treatment of choice when adequate asthma control cannot be achieved despite the Step 5 drug treatment, as outlined in the NVL for Asthma or the S2k Asthma Guideline.

Currently, the following monoclonal antibodies are approved for use in children (Table 1, approval criteria from the NVL)

1. Anti-IgE antibodies: omalizumab (from 6 y of age)
2. Anti-IL-4/IL-13 receptor antibodies: dupilumab (in the indication asthma from 6 y of age)
3. Anti-IL-5 antibodies: mepolizumab (from 6 y of age; in Switzerland from 12 y of age)
4. Anti-TSLP antibodies: tezepelumab (from 12 y of age, in Switzerland from 18 years of age)

Other monoclonal antibodies approved in Germany for adults are reslizumab (anti-IL-5 antibody) and benralizumab (anti-IL-5 receptor antibody), but these are not discussed further due to the lack of approval under the age of 18 years and a lack of evidence on efficacy and safety in paediatric patients. Biologics currently used in studies for the treatment of severe asthma in children and adolescents are discussed in Chapter 5. Future treatment options for severe asthma.

An overview of the mechanism of action, the clinical evidence and a compilation of the relevant paediatric studies for the approved biologics is provided below.

Anti-IgE antibodies (omalizumab) Omalizumab is a monoclonal Anti-IgE-antibody and is approved for children aged 6 years and older with severe allergic asthma. The prerequisites are perennial sensitization, a total IgE of 75–1500 kU/l, frequent exacerbations despite ICS/LABA, and impaired lung function (≥ 12 years only).

Table 3 (extract from original in guideline) Typical comorbidities and diagnostics

Comorbidity	Diagnostic
Allergic rhinitis	Rhinoscopy and nasal provocation if necessary
Atopic dermatitis	Clinical inspection and dermatologist if necessary
Food allergy	Component diagnostics and provocation
Reflux	pH-metry and endoscopy
Sinusitis/polyps	Endoscopy and ENT consultation if necessary
Obesity	BMI progression and rehab if necessary
Sleep apnea	Polysomnography
DRS	Stress tests and laryngoscopy

Abbreviation: BMI, body mass index.

Add-on omalizumab significantly reduced exacerbations and oral steroid administration. Efficacy and safety have been proven in several RCTs and long-term studies.³¹

Anti-IL-4/IL-13 receptor antibody (dupilumab) Dupilumab blocks IL-4R α and thereby inhibits type 2 inflammation centrally. It is approved from 6 years of age for severe asthma with type 2 inflammation (eosinophils $\geq 150/\mu\text{l}$ and/or FeNO ≥ 20 ppb). The VOYAGE study showed significant reductions in exacerbations and rapid, sustained improvements in lung function. Patients with high IgE concentrations or concomitant atopic dermatitis also benefit. It is applied subcutaneously every 2 or 4 weeks depending on weight and has also shown good efficacy and safety in long-term observation.^{32–35}

Anti-IL-5 antibody (mepolizumab) Mepolizumab is an anti-IL-5-antibody which is approved from 6 years of age for severe eosinophilic asthma with ≥ 150 eosinophils/ μl . It has shown moderate efficacy with reducing exacerbations and the need for OCS. Dosing is subcutaneous every 4 weeks depending on weight. Studies have also demonstrated efficacy and safety in children with multiple comorbidities.^{36,37}

Anti-TSLP antibody (tezepelumab) Tezepelumab inhibits TSLP, an early epithelial alarmin. It is approved from the age of 12 years, regardless of type 2 phenotype. In (mostly adult) studies, it significantly reduced exacerbations, even in patients with low eosinophils and FeNO. It is administered subcutaneously on a monthly basis.^{38,39}

Therapy of different asthma phenotypes

The choice of biologics depends on phenotype, biomarkers and comorbidities. Reliable comparative studies are lacking, but patient-specific criteria for omalizumab and dupilumab can be derived. Omalizumab is particularly effective in allergic and T2-high asthma with relevant sensitization. Dupilumab shows advantages in AD, high IgE or low lung function. The data situation for mepolizumab and tezepelumab is limited^{36,40} (**Fig. 3**).

Recommendation 26: Only antibodies approved for use in children, with safety demonstrated in clinical studies, should be used.

Recommendation 27: Eosinophils, IgE, sIgE/prick test, FEV₁ and FeNO should be determined for selection.

Recommendation 28: Therapy selection should be based on the individual phenotype.

Statement 1: Omalizumab and dupilumab are the first choice for uncontrolled asthma.

Recommendation 29: For sensitization to perennial allergens and suitable IgE, omalizumab is used.

Recommendation 30: For AD, IgE > 1500 or PN is primarily dupilumab.

Statement 2: No recommendation can currently be made for mepolizumab and tezepelumab.

Recommendation 31: In the case of isolated eosinophilia without AD/allergy, consider a therapy trial with mepolizumab.

Therapy evaluation under biologics The response to treatment should be assessed after 3 months at the earliest and a non-response after 6 months at the latest. This includes symptoms, exacerbations and lung function. Duration of therapy in the case of response: at least 12, preferably 24 months.

Reduction and discontinuation of biologics To date, there have been no evidence-based recommendations on the optimal duration of therapy with biologics in children with severe asthma. Clinical experience exists in particular for omalizumab. A gradual dose reduction with extension of the injection intervals can lead to a discontinuation attempt if the asthma remains well controlled.

Recommendation 32: After starting a biologic, treatment should initially be continued for at least 3 months before the response can be assessed.

Recommendation 33: In the case of a positive response to a biologic, therapy should be continued for at least 12, preferably 24 months before discontinuation should be considered.

Recommendation 34: In the case of a positive response to a biologic, patients on high-dose ICS therapy should initially be switched to continuous therapy with medium-dose ICS.

Very young children and preschool children (1–5 y)

Obstructive airway diseases are common in this age group and are difficult to distinguish from asthma and are often triggered by infections. Early phenotyping using eosinophils, specific IgE and family history can point towards asthma. If asthma is diagnosed, ICS is the medication of choice; montelukast is an alternative treatment but has shown less efficacy and potential neuropsychiatric side effects. Continuous ICS therapy should be considered in the case of frequent exacerbations, whereby the dose and effect must be checked regularly. Due to the lack of evidence, ICS/LABA combination is not recommended as the standard, but is considered justifiable as “off-label” medication in individual cases before the age of 4 years.^{41–47}

Recommendation 35: If asthma is insufficiently controlled with ICS at a medium dose, treatment with LABA as add-on to ICS can be tried before age 4 after differential diagnoses have been ruled out. Treatment responses should be reviewed after 6 weeks at the latest. Parents should be informed about off-label use.

Rehabilitation

Inpatient rehabilitation is a central component of the management of severe or difficult asthma in children and adolescents. It is

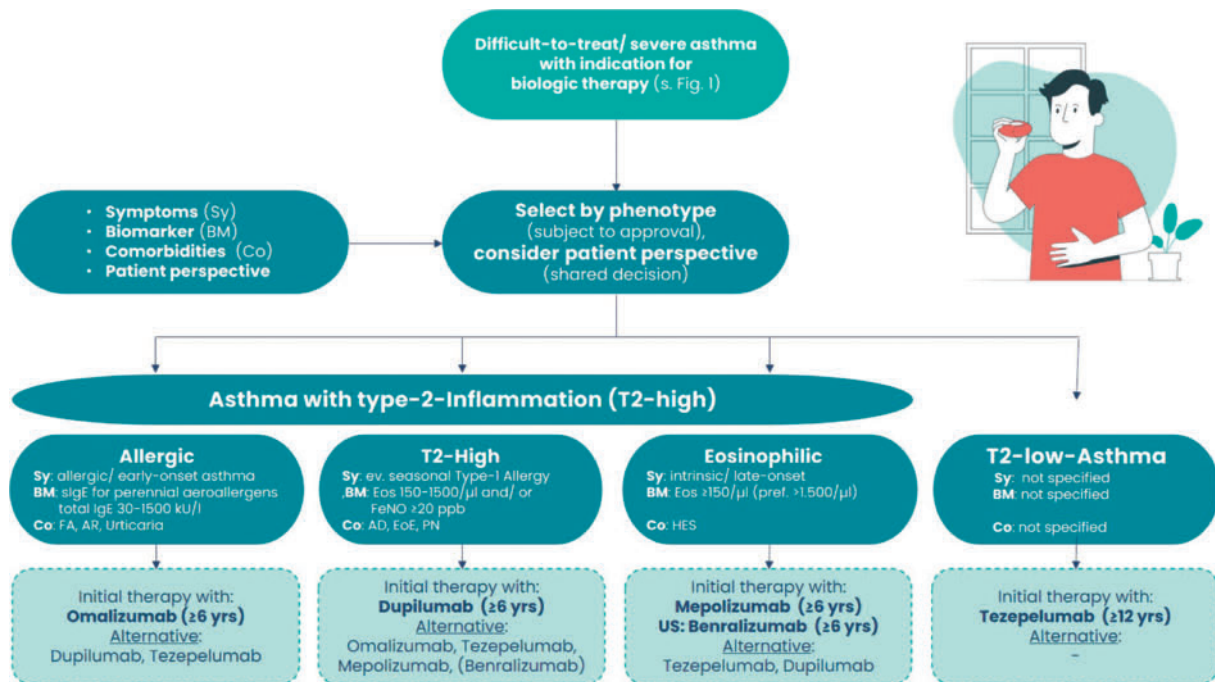


Fig. 3 Initial therapy with biologics based on endotyping. AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy [rerif].

indicated in cases of impaired function, activity or social participation, inadequate control despite guideline-compliant therapy or frequent exacerbations. In addition to medical treatment, training, psychosocial care and self-management support are key components. The programmes must be interdisciplinary, standardized and conform to guidelines. Successful rehabilitation requires structured networking with general practitioners, specialist centres and psychosocial support. Aftercare services within the framework of the Flexible Retirement Act are becoming increasingly important.^{48–50}

Recommendation 36: For all children and adolescents with difficult asthma, inpatient rehabilitation should be considered before treatment at therapy level 5 or 6 (NVL) or 4 or 5 (GINA) or in the case of recurrent asthma exacerbations or persistently poor asthma control, especially in the case of disease-related restrictions in activity and social participation. The inpatient measure should be carried out in a specialized facility as part of a standardized multidisciplinary intervention including asthma training measures.

Transition of care

The structured transition of adolescents with severe asthma is insufficiently established in German-speaking countries. A lack of concepts and gaps in care often lead to discontinuation of care. International programs, e.g., “ReadySteadyGO” or the Zurich transition program, show successful approaches with a step-by-step approach, starting in early adolescence. Success factors are interdisciplinary cooperation, structured support, training and involvement of the family. The aim is to provide continuous specialist care and ensure the flow of information between paediatric and adult medicine.^{51,52}

Recommendation 37: The paediatric and adolescent pulmonologist managing an adolescent living with severe asthma should establish collaboration with pulmonologists as part of the transition.

Recommendation 38: Adolescents with severe asthma should be prepared early for transition to adult respiratory care.

Recommendation 39: A medical discharge summary should be prepared for the transition.

Future therapies for severe asthma in children

Future therapies will focus on new biologics that address specific signalling pathways such as TSLP or IL-33. Tezepelumab is the first TSLP-targeted compound with a broad anti-inflammatory effect. Other substances such as itepekimab (IL-33), risankizumab (IL-23) or fevipirant (PGD2) are currently being tested, but have so far shown limited efficacy. The challenge lies in the targeted selection of the appropriate biologic based on individual pathomechanisms. There is a lack of reliable biomarkers and studies suitable for children. Most new active substances are initially developed for adults; children remain underrepresented in research^{53–57} (**Fig. 4**).

Perspectives and practice recommendations

This guideline for the management of severe asthma in children and adolescents provides a structured basis for the diagnosis, treat-

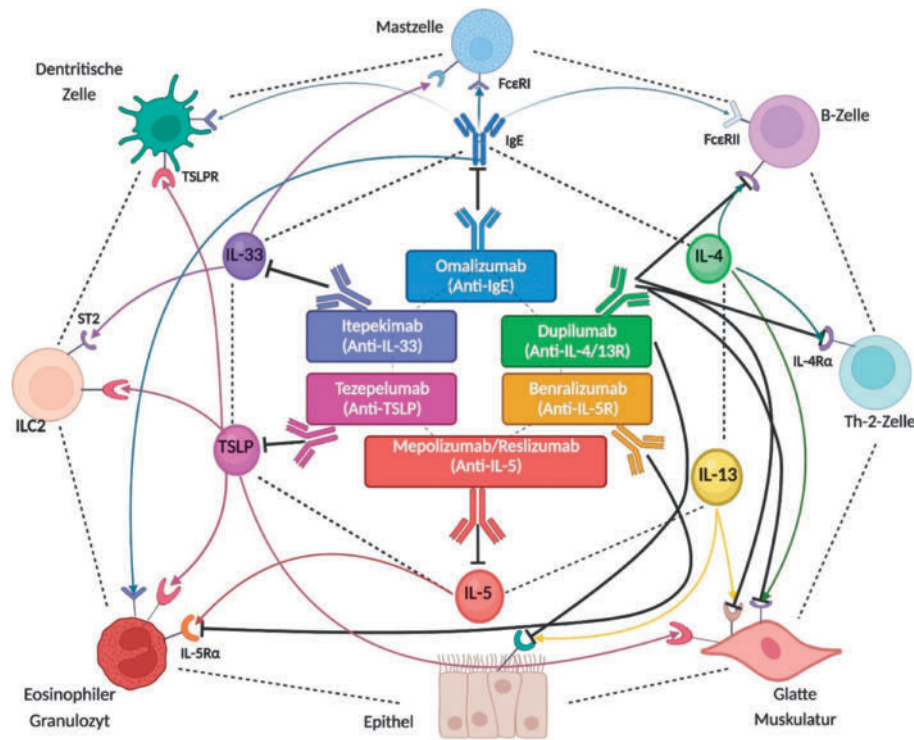


Fig. 4 Schematic representation of the molecular mechanisms and target structures of various biologics currently available or under development for use in severe type 2 asthma. Source: ref.⁵⁷ [rerif].

ment, and care of this patient group. The concluding chapter summarizes the most important findings, identifies open questions, and outlines perspectives for research and clinical practice.

Conclusion for practice

- Asthma is the most common chronic respiratory disease in children and adolescents; most patients achieve good control with guideline-based treatment.
- Despite adequate treatment, a relevant proportion of patients suffer from persistent symptoms, frequent exacerbations and reduced quality of life—this group accounts for up to 90 % of total medical costs.
- The precise distinction between difficult-to-treat asthma and genuinely severe asthma is crucial for diagnosis and management.
- Patients with severe asthma require particularly careful, multidimensional diagnostics and continuous, and structured care.
- In suitable patients, targeted therapy with modern biologics based on phenotyping and biomarker profile should be considered.

Author affiliations

- 1 Bethel Children Center – Department of Pediatrics, Protestant Hospital Bethel, Bielefeld, Germany
- 2 University Hospital OWL, Bielefeld University, Bielefeld, Germany
- 3 Bethel Children's Center, Protestant Hospital Bethel, Bielefeld, Germany
- 4 KinderPneumologieDerichs, Pediatric Pneumology and Allergology, Hannover, Germany
- 5 Paediatrics, Medical University of Graz, Graz, Austria
- 6 Clinic for children and adolescents, University Hospital Augsburg, Augsburg, Germany
- 7 Pulmonology, University Children's Hospital Zürich, Zürich, Switzerland
- 8 Clinic and Polyclinic for Pediatric and Adolescent Medicine, Barmherzige Brüder Klinik St Hedwig Regensburg, Regensburg, Germany
- 9 University Clinic for Pediatrics, Inselspital Universitätsspital Bern, Bern, Switzerland
- 10 Clinic for Pediatrics with a focus on pneumology, immunology, and intensive care medicine, Charité University Hospital Berlin, Berlin, Germany
- 11 Department of Paediatrics and Adolescent Medicine- Paediatric Cardiology, Intensive Care Medicine and Pneumology, University Medical Center Göttingen, Göttingen, Germany
- 12 Pulmonology, University Children's Hospital Zürich, Zürich, Switzerland
- 13 Dr. von Hauner Children's Hospital, LMU Hospital, Munich, Germany
- 14 Pediatric pulmonology and neonatology, Hannover Medical School, Hanover, Germany

- 15 Medical Care Center GmbH, Friedrichshafen Hospital, Friedrichshafen, Germany
- 16 Department of Pulmonary Medicine, University Hospital Essen, Essen, Germany
- 17 Pediatric Department, University Hospital Carl Gustav Carus, Dresden, Germany
- 18 Department of Pediatrics, Vienna Healthcare Group – Campus Ottakring Hospital, Vienna, Austria
- 19 Institute for Respiratory Diseases, Medaimun GmbH, Frankfurt, Germany
- 20 Center for Pediatric and Adolescent Medicine, University Hospital of Düsseldorf, Düsseldorf, Germany
- 21 Pediatrics, Evangelical Hospital Düsseldorf Medical Clinic, Düsseldorf, Germany

Statements and additional information

Conflict of Interest The authors declare that they have no conflict of interest.

Contributors' Statement Eckard Hamelmann: project administration and writing—original draft. Christina Schorlemer: project administration. Ernst Eber: writing—original draft. Michael Gerstlauer: writing—original draft. Andreas Jung: writing—original draft. Michael Kabisch: writing—original draft. Matthias Volkmar Kopp: writing—original draft. Susanne Lau: writing—original draft. Christiane Lex: writing—original draft. Alex Möller: writing—original draft. Bianca Schaub: writing—original draft. Nicolaus Schwerdt: writing—original draft. Thomas Spindler: writing—original draft. Christian Taube: writing—original draft. Christian Vogelberg: writing—original draft. Angela Zacharasiewicz: writing—original draft. Stefan Zielen: writing—original draft. Antje Schuster: project administration and writing—original draft. Monika Gappa: project administration and writing—original draft.

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Zusammenfassung

Hintergrund Asthma bronchiale ist die häufigste chronische Atemwegserkrankung im Kindes- und Jugendalter. Während der Großteil der Patient:innen unter leitliniengerechter Therapie gut behandelt werden kann, leidet eine relevante Subgruppe an schwerem oder schwer behandelbarem Asthma mit eingeschränkter Lebensqualität und hoher Krankheitslast.

Ziel Diese S1-Leitlinie zielt darauf ab, schweres Asthma im Kindes- und Jugendalter klar zu definieren, eine strukturierte diagnostische und therapeutische Herangehensweise zu fördern und konkrete Empfehlungen für das Management, einschließlich des Einsatzes von Biologika, zu geben.

Methoden Die Leitlinie wurde unter Federführung der Gesellschaft für Pädiatrische Pneumologie (GPP) gemäß AWMF-Regelwerk erstellt. Grundlage war ein systematischer Literaturreview relevanter nationaler und internationaler Empfehlungen. Ein multidisziplinäres Expertengremium stimmte alle Empfehlungen konsensbasiert ab.

Ergebnisse Im Mittelpunkt steht ein mehrstufiges diagnostisches Vorgehen zur Differenzierung zwischen schwer behandelbarem und genuin schwerem Asthma. Es werden Kriterien zur Therapieadhärenz, Komorbiditätserfassung und phänotypspezifischer Auswahl von Biologika dargestellt. Weitere Themen sind Monitoring, Rehabilitation, Transition und zukünftige Therapien. Empfehlungen zur Anwendung bestehender und neuer monoklonaler Antikörper basieren auf aktueller Evidenz.

Schlussfolgerung Kinder mit schwerem Asthma benötigen eine strukturierte, interdisziplinäre Versorgung. Eine frühe phänotypbasierte Therapie mit Biologika sowie flächendeckende Registerdaten und patientenorientierte Versorgungspfade sind erforderlich, um die Prognose dieser Patientengruppe zu verbessern.

Schlüsselwörter Schweres Asthma, Kindliches Asthma, Biologika, Asthmanagement, Leitlinie

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Notice

This article was changed according to the Correction on March 30th, 2026.

Erratum

In the above mentioned article, the name of an author has been added. The correct list of authors is: Eckard Hamelmann, Christina Schorlemer, Nico Derichs, Ernst Eber, Michael Gerstlauer, Andreas Jung, Michael Kabisch, Matthias Volkmar Kopp, Susanne Lau, Christiane Lex, Alex Möller, Bianca Schaub, Nicolaus Schwerk, Thomas Spindler, Christian Taube, Christian Vogelberg, Angela Zacharasiewicz, Stefan Zielen, Antje Schuster, Monika Gappa.