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REVIEW

Biologics in severe pediatric asthma: advances and unmet needs

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ABSTRACT

Severe pediatric asthma is defined as asthma that remains uncontrolled despite adherence to optimized high-dose inhaled corticosteroids (ICS) with long-acting β2-agonists (LABA) and systematic management of modifiable factors, or that worsens upon treatment de-escalation. Affecting approximately 3% of European children, this condition imposes substantial clinical and socioeconomic burden due to frequent exacerbations, persistent symptoms, impaired lung function, and elevated healthcare utilization, emergency department visits and hospitalizations. Advances in the understanding of asthma immunopathology have enabled the development of targeted biologic therapies, including omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab, which have improved disease control and reduced systemic corticosteroid requirements. These agents decrease exacerbation frequency, enhance lung function, and facilitate more individualized, biomarker-guided treatment strategies. Selection of therapy is guided by clinical phenotype,

inflammatory endotype, and biomarkers such as blood eosinophil count, fractional exhaled nitric oxide (FeNO), and IgE levels. While therapeutic selection relies heavily on clinical phenotype and biomarker profiling, significant challenges persist, including high treatment costs, inequitable access, immunogenicity, and limited pediatric data to define remission, optimal treatment duration, and discontinuation strategies. Multidisciplinary, phenotype-driven care and long-term monitoring remain essential to maximize outcomes. Future research should focus on refining predictive biomarkers, expanding clinical trial diversity, and standardizing definitions of treatment success and remission to guide earlier, precision-based interventions in children with severe asthma.

IMPACT STATEMENT

Precision biologic therapy is redefining severe pediatric asthma, though durable remission strategies and validated biomarkers for treatment selection remain insufficiently defined.

KEY WORDS

Severe pediatric asthma; biologics; precision medicine.

INTRODUCTION

According to the 2025 Global Initiative for Asthma (GINA), severe asthma is defined as asthma that remains uncontrolled despite verified adherence to optimized high-dose inhaled corticosteroids (ICS) in combination with long-acting β2-agonists (LABA), appropriate inhaler technique, and management of modifiable risk factors, or that worsens when high-dose therapy is reduced (1).

According to recent epidemiological data from a systematic review and meta-analysis, approximately 3% of the pediatric population in Europe is affected by severe asthma (2).

Severe asthma in children is associated with elevated morbidity and increased healthcare demands, including frequent hospitalizations, emergency department visits, and prolonged pharmacotherapy, leading to considerable socioeconomic burdens. Despite optimized therapy, many children with severe asthma continue to experience persistent symptoms, recurrent exacerbations, and impaired lung function (3, 4).

Advances in the understanding of asthma immunopathology have led to the development of targeted biologic therapies.

Monoclonal antibodies directed against specific inflammatory pathways, such as immunoglobulin E (IgE; omalizumab), interleukin-5 (IL-5; mepolizumab), IL-5 receptor alpha (IL-5Rα; benralizumab), and the interleukin-4/interleukin-13 (IL-4/IL-13) axis (dupilumab), have demonstrated clinical efficacy in reducing exacerbations, improving lung function, and decreasing dependence on systemic corticosteroids (5, 6).

Emerging evidence also highlights the role of airway epithelium as a key initiator of inflammatory responses in asthma pathophysiology. Biologics targeting epithelial cytokines (alarmins), such as thymic stromal lymphopoietin (TSLP; tezepelumab), have shown substantial efficacy in improving symptom control in severe asthma. However, further studies are needed to fully elucidate their mechanisms of action and long-term clinical impact (7).

The selection of biologic therapy is primarily guided by the patient's clinical phenotype and underlying endotype, in conjunction with a comprehensive evaluation of factors contributing to poor disease control. In this context, validated biomarkers, including blood eosinophil count (BEC), fractional exhaled nitric oxide (FeNO), markers of allergic sensitization, and serum IgE levels, play a central role in identifying patients most likely to benefit from specific biologic agents (8). The implementation of biomarker-driven biologic therapies has substantially transformed the management of severe asthma, leading to significant improvements in disease control and meaningful reductions in exacerbation frequency. Despite these advances, important knowledge gaps remain.

A comprehensive literature search was conducted to evaluate the current evidence on biologic therapies for severe pediatric asthma. The PubMed database was searched using predefined combinations of Medical Subject Headings terms and keywords, including "severe pediatric asthma", "biologic therapy" and "monoclonal antibodies" as well as the names of individual agents (*e.g.*, omalizumab, mepolizumab, benralizumab, dupilumab, tezepelumab). Additional search terms addressed key domains of interest, including mechanisms of action, clinical efficacy, safety, and criteria for patient selection. Publications from 2000 to 2026 were eligible for inclusion and encompassed original research articles, randomized controlled trials (RCTs), observational studies,

systematic reviews, meta-analyses, international clinical practice guidelines, and reviews. Relevant articles were further identified through manual screening of reference lists. Given the substantial heterogeneity across studies with respect to design, patient populations, biologic agents evaluated, and outcome measures, quantitative synthesis through meta-analysis was not considered appropriate. Consequently, a narrative synthesis was performed, enabling an integrated and critical appraisal of the available evidence and providing a structured overview of the current and emerging role of biologic therapies in the management of severe pediatric asthma.

FROM ASTHMA PATHOPHYSIOLOGY TO SEVERE DISEASE ENDOTYPES

Although severe asthma does not represent a distinct pathophysiological entity, it reflects the most complex end of the asthma spectrum, characterized by persistent inflammation, greater biological heterogeneity, and reduced responsiveness to conventional therapy. Understanding the immunopathogenesis of asthma is therefore essential to explain the mechanisms underlying severe disease and the rationale for biologic therapies (1).

A variety of factors, including allergens, infections, obesity, hormonal influences, tobacco smoke exposure, exercise, cold air, and genetic mutations (*e.g.*, ADAM33, PHF11, DPP10, GPRA), have been shown to contribute to chronic airway inflammation, ultimately leading to airway obstruction, remodeling and hyperresponsiveness (9).

The immune dysregulation underlying asthma, and driving the different inflammatory endotypes observed in severe disease, results from activation of both the innate and adaptive immune systems, resulting in two broad inflammatory classifications: type 2 (T2)-high and T2-low inflammatory pathways (10).

In children, T2-high inflammation represents the predominant endotype. Upon exposure to inhaled allergens, naïve T cells differentiate into Th2 cells, which subsequently release cytokines such as IL-4, IL-5, IL-9, and IL-13. IL-4, IL-9, and IL-13 promote B-cell activation and IgE production, which in turn triggers mast cell degranulation with the release of histamine and leukotrienes, leading to bronchoconstriction. IL-5 plays a central role in eosinophil maturation, while IL-9 and IL-13 further contribute to mucus hypersecretion (9).

Recent studies have underscored the critical role of the epithelial barrier in asthma pathophysiology. Indeed, dysregulation of this barrier facilitates allergen penetration and promotes the release of alarmins, including TSLP, IL-25, and IL-33. TSLP activates dendritic cells, which drive the differentiation of naïve T cells into Th2 cells. The alarmins IL-25 and IL-33 further amplify T2 inflammation by activating group 2 innate lymphoid cells (ILC2s), as well as mast cells, eosinophils, and basophils (11, 12).

Although less prevalent, T2-low asthma endotypes are observed in both adults and children and are increasingly recognized as clinically significant. T2-low asthma is primarily driven by the activation of T helper (Th)1 and Th17 cells, leading to the release of proinflammatory cytokines such as IL-17, IL-6, and tumor necrosis factor-α (TNF-α). This inflammatory pattern is typically associated with neutrophilic or paucigranulocytic airway inflammation, reduced responsiveness to corticosteroids, and a more challenging clinical course (13, 14).

Advances in asthma immunology have enabled a more precise characterization of severe asthma endotypes, allowing biomarker-guided selection of biologic therapies. Biomarkers play a central role in differentiating endotypes and guiding targeted treatment. In clinical practice, BEC, FeNO, and serum total IgE are the most widely used markers for identifying both T2-high and T2-low asthma. Notably, however, 30-50% of patients demonstrate variability in T2 status over time (14).

BEC ≥ 150 cells/μL indicates T2 inflammation and is associated with asthma exacerbations. Alone or in combination with elevated FeNO (≥ 20 ppb in children), it predicts high airway inflammation, poor asthma control, increased risk of severe exacerbation, and favorable responsiveness to biologics targeting the IL-5 and IL-4/IL-13 pathways (15).

Serum total IgE levels are critical for determining the appropriate therapeutic dose of omalizumab and are currently under investigation for treatment monitoring. Allergen-specific IgE levels, however, are more closely associated with asthma severity. Emerging biomarkers, including periostin, TSLP, natural killer cells, urinary eicosanoids, and specific microRNAs, are being evaluated for their potential to further refine pediatric asthma endotyping (8).

Systemic IL-6 has also been proposed as a biomarker for non-T2 asthma phenotypes; however, its clinical utility is limited by lack of disease specificity, as elevated IL-6 levels may occur in other inflammatory conditions (16).

BIOLOGIC THERAPIES APPROVED FOR SEVERE PEDIATRIC ASTHMA

Omalizumab

Omalizumab represents the first humanized monoclonal antibody introduced into clinical practice within the field of allergology (17). It was initially authorized in 2003 by the U.S. Food and Drug Administration (FDA) for the management of moderate-to-severe persistent allergic asthma in patients aged 12 years and older who had a positive skin prick test (SPT) or in vitro reactivity to a perennial aeroallergen, and whose symptoms remain uncontrolled despite high-dose inhaled ICS plus additional controller therapy (18). The therapeutic indication was subsequently expanded in 2009 to include children aged ≥ 6 years in European countries, and this extension was later adopted in the United States as well (19-21). According to the National Institute for Health and Care Excellence (NICE), omalizumab is recommended as an add-on therapy for patients ≥ 6 years old with severe persistent allergic (IgE-mediated) asthma who have a positive SPT or serum-specific IgE, a total serum IgE level between 30-1500 IU/mL, and require frequent oral corticosteroids (OCS) courses (≥ 4 in the previous 12 months) despite optimized treatment (22).

Omalizumab is administered subcutaneously every 2-4 weeks depending on the patient's total serum IgE levels and body weight (23).

Omalizumab binds to the Cε3 domain of circulating IgE, forming inactive immune complexes that do not trigger complement activation. This interaction markedly reduces free serum IgE levels and prevents IgE from binding to high- (FcεRI) and low-affinity (FcεRII/CD23) receptors on effector cells such as mast cells, basophils, and dendritic cells. Consequently, receptor expression and mediator release are downregulated. Omalizumab also targets membrane-bound IgE on B cells, disrupting IgE-CD21 and soluble CD23 signaling, thereby inhibiting IgE synthesis and inducing apoptosis of IgE-producing B cells. Beyond modulating allergic inflammation, omalizumab enhances antiviral immunity by restoring Toll-like receptor function and interferon (IFN)-α production in plasmacytoid

dendritic cells, which are often impaired in allergic asthma with high IgE levels. Additionally, omalizumab reduces IL-33 concentrations, leading to decreased expression of proinflammatory cytokines such as IL-6, IL-1β, and TNF-α, ultimately contributing to airway inflammation control (24). The efficacy of omalizumab in severe pediatric asthma has been established through both RCTs and real-world studies.

A Cochrane systematic review of 25 RCTs published up to 2013 – including studies involving children aged 5–12 years and adolescents aged 12–17 years – demonstrated a significant reduction in asthma exacerbation rates among patients receiving omalizumab compared with placebo. Omalizumab-treated patients experienced fewer exacerbations requiring OCS, lower hospitalization rates, and a reduced need for ICS. The therapy also increased the likelihood of discontinuing or tapering ICS doses (25).

Several individual RCTs have further confirmed these findings. Milgrom *et al*. reported in 334 children with moderate-to-severe allergic asthma that omalizumab led to a complete discontinuation of ICS in many cases and markedly reduced the frequency of acute exacerbations (26). In the IA-05 trial, which included 627 pediatric patients, omalizumab reduced the annual exacerbation rate by approximately 40%-50% compared with placebo, particularly in those receiving high-dose ICS plus LABA (27). Similarly, the Inner-City Anti-IgE Therapy for Asthma (ICATA) study demonstrated reductions in symptom days, exacerbations, and treatment intensity over a 60-week period. Importantly, post hoc analyses indicated that omalizumab mitigated seasonal peaks in exacerbations often associated with viral infections (28).

Real-world evidence supports the durability of these benefits. In a French multicenter cohort of 104 children, one year of omalizumab therapy reduced severe exacerbations by more than two-thirds and hospitalizations by nearly 90%, while improving lung function and allowing ICS dose reduction. These improvements persisted in over 80% of patients after two years (29). Comparable outcomes were observed in an Italian multicenter study involving 47 children, which reported substantial declines in exacerbations and hospitalizations, complete cessation of maintenance OCS, and improved FEV_1 values (30).

Biomarker analyses suggest that omalizumab achieves its greatest efficacy in patients with elevated T2 inflammation. Patients with higher FeNO and BEC values showed the most pronounced reductions in exacerbation rates, whereas baseline total or specific IgE levels were poor predictors of response (31).

Omalizumab has also been shown to improve lung function, particularly in adolescents and in patients with elevated T2 biomarkers. Positive predictors of therapeutic response include polysensitization to multiple allergens and higher total IgE levels, while weaker responses have been associated with older age, recent exacerbations, lower baseline FEV_1, and comorbidities such as obesity or gastroesophageal reflux (32, 33).

Discontinuation studies indicate that clinical benefits may persist after treatment withdrawal in selected patients. In a large real-world analysis including over 19,000 patients, most children maintained asthma control for up to three years after omalizumab discontinuation, with stable hospitalization and corticosteroid use (34). Smaller prospective and retrospective pediatric studies further confirmed sustained improvements in lung function, exacerbation rates, and quality of life (QoL) for at least one year following therapy discontinuation (35, 36).

Overall, omalizumab demonstrates consistent efficacy, durability, and safety in children and adolescents with severe allergic asthma. The most common adverse events are mild injection-site reactions, while serious events are rare (37).

Ongoing trials, including the Preventing Asthma in high Risk Kids (PARK) study, are exploring whether early omalizumab intervention in high-risk toddlers may prevent or modify asthma development, potentially expanding the therapeutic scope of anti-IgE therapy in pediatric populations (38).

Mepolizumab and benralizumab

Mepolizumab is a humanized IgG1κ monoclonal antibody approved by both the FDA and the European Medicines Agency (EMA) as an add-on maintenance therapy for children aged six years and older with severe eosinophilic asthma (39, 40). Eligibility criteria typically include BEC ≥ 300 cells/μL with frequent systemic corticosteroid-requiring exacerbations (≥ 4 in the past year) or

prolonged daily corticosteroid use (equivalent to ≥ 5 mg/day of prednisolone for six months) or, alternatively, frequent exacerbations or chronic corticosteroid use, or BEC ≥ 400 cells/μL with at least three corticosteroid-treated exacerbations in the preceding year (41).

The recommended dosing regimen consists of 40 mg subcutaneously every four weeks for children aged 6-11 years and 100 mg for those aged 12 years and above, administered via prefilled syringe (23).

Mepolizumab binds IL-5, preventing its interaction with the IL-5 receptor α-subunit (IL-5Rα) on eosinophils. By neutralizing IL-5 activity, mepolizumab reduces eosinophil maturation, recruitment, and survival, thereby attenuating eosinophilic airway inflammation. Furthermore, beyond reducing eosinophil counts, mepolizumab may modulate antiviral immunity. Indeed, eosinophils contribute to antiviral defense by releasing ribonucleases such as eosinophil-derived neurotoxin and eosinophil cationic protein, which degrade viral RNA, limiting viral replication and spread. However, excessive eosinophilic inflammation can impair immune balance and exacerbate respiratory viral infections. By restoring the ratio of IFN-γ to IL-5 expression, mepolizumab may enhance antiviral responses while suppressing tissue-damaging inflammation (24).

An open-label pharmacokinetic study involving children aged 6-11 years demonstrated that 12 weeks of subcutaneous treatment achieved substantial reductions in BEC – approximately 85% to 90% – comparable to reductions seen in adolescents and adults, confirming consistent pharmacological activity across age groups (42).

The pivotal Mechanisms Underlying Asthma Exacerbations Prevented and Persistent with Immune-Based Therapy: A Systems Approach–Phase 2 (MUPPITS-2) trial, a multicenter RCT involving 290 urban children aged 6-17 years, provided strong evidence of mepolizumab's clinical efficacy. Treatment led to a 27% reduction in the annualized rate of asthma exacerbations compared with placebo. Transcriptomic profiling of nasal samples revealed downregulation of eosinophil-associated and T2 inflammatory gene modules, while pathways linked to epithelial activation (including IL-33 signaling) remained active in a subset of non-responders. These findings indicate that persistent, non-eosinophilic inflammation may underlie residual disease activity despite IL-5 blockade (43).

Further analyses from Fricker *et al*. and Vultaggio *et al*. showed that mepolizumab selectively depletes inflammatory eosinophils expressing low CD62L, while sparing subsets involved in tissue homeostasis, suggesting immune rebalancing rather than complete eosinophil depletion (44, 45).

The Sputum CyTOF Substudy (SCOUT), nested within MUPPITS-2, used high-dimensional cytometry to characterize eosinophil diversity in induced sputum. Three eosinophil subpopulations – CD62L low, intermediate, and high – were identified. Children who experienced exacerbations despite mepolizumab exhibited higher proportions of CD62L-intermediate and -high eosinophils, expressing increased activation markers (CD69, CCR3) and secreting IL-5, IL-13, and TNF-α. These data suggest that airway-resident, activated eosinophil subsets may drive breakthrough exacerbations even when circulating eosinophils are suppressed (46).

A subsequent systems-level analysis of MUPPITS-2 participants confirmed that, under mepolizumab, residual exacerbations were primarily associated with non-T2 inflammatory signatures, including macrophage activation, epithelial stress responses, and mucus hypersecretion. Distinct molecular exacerbation patterns were also identified based on the presence or absence of viral infection, underscoring the complexity of asthma endotypes in children (47).

Long-term extension studies demonstrate that mepolizumab maintains a favorable safety and tolerability profile in pediatric patients with severe eosinophilic asthma. Reported adverse events are generally mild and transient, most commonly upper respiratory infections and headaches. Serious adverse reactions are rare, and no cases of anaphylaxis or systemic hypersensitivity have been documented (48).

Regarding benralizumab, it is an IL-5Rα–directed cytolytic monoclonal antibody (IgG1κ) approved by the FDA as an add-on maintenance treatment for patients aged 6 years and older with severe eosinophilic asthma. In contrast, the EMA and the NICE guidelines currently approve its use only in adults (≥ 18 years) who meet at least one of the following criteria: BEC ≥ 0.3 × 10^9/L with ≥ 4 exacerbations requiring OCS in the previous 12 months or maintenance OCS therapy equivalent to ≥ 5 mg/day of prednisolone over the past 6 months; or BEC ≥ 0.4 × 10^9/L with ≥ 3 exacerbations in the preceding year (49-51).

According to the FDA-approved dosing regimen, children aged 6-11 years weighing ≥ 35 kg should receive 30 mg subcutaneously, while those weighing < 35 kg should receive 10 mg. Treatment begins with an induction phase of three doses administered every four weeks, followed by maintenance dosing every eight weeks (23).

Benralizumab exerts its therapeutic effect by binding to the IL-5Rα on eosinophils and basophils, triggering antibody-dependent cell-mediated cytotoxicity that leads to rapid and sustained eosinophil depletion (24).

The FDA approval for pediatric use was supported by data from the TATE study, a 48-week open-label trial that assessed the pharmacokinetic and pharmacodynamic properties of benralizumab in 28 children with severe eosinophilic asthma. The study demonstrated a 50% reduction in asthma exacerbations and notable improvements in symptom control. Benralizumab exhibited a favorable safety profile, with the most frequently reported adverse events being mild upper respiratory tract infections and localized injection-site reactions (52).

Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody approved by both the FDA and the EMA as an add-on maintenance therapy for moderate-to-severe asthma in patients aged 6 years and older with an eosinophilic phenotype or OCS-dependent asthma (53, 54). According to the NICE guidelines, eligibility criteria include a history of ≥ 4 OCS-treated asthma exacerbations in the previous year, failure or ineligibility for anti–IL-5 therapy, BEC ≥ 0.15 × 10^9/L, and FeNO ≥ 25 ppb (55). The dosing is based on body weight, age, and OCS use (23).

Dupilumab acts by binding to and blocking the IL-4 receptor α-subunit (IL-4Rα), thereby inhibiting signaling through both IL-4 and IL-13 pathways. This dual inhibition downregulates the molecular cascade responsible for T2 inflammation, leading to reductions in eosinophilic inflammation, mucus hypersecretion, IgE class switching, bronchial hyperresponsiveness, and airway remodeling. By suppressing IL-4Rα signaling, dupilumab decreases biomarkers of T2 inflammation, including blood eosinophil levels and FeNO. In addition to its anti-inflammatory effects, dupilumab may exert

immunomodulatory and antiviral benefits by shifting the immune balance from a Th2-dominant to a Th1-skewed profile, thereby enhancing IFN-γ production and improving antiviral defenses (24).

The Phase III VOYAGE trial, a pivotal study in children aged 6–11 years with uncontrolled moderate-to-severe asthma, demonstrated that dupilumab significantly reduced the annualized rate of severe asthma exacerbations. After 52 weeks, 78% of patients receiving dupilumab remained exacerbation-free, compared with 60% in the placebo group. Improvements in percent predicted FEV_1 were observed as early as week 2 and were maintained throughout the treatment period. The benefits were most pronounced in children with T2-high asthma, particularly those with baseline eosinophils ≥ 300 cells/μL or FeNO ≥ 20 ppb, underscoring the predictive value of these biomarkers for dupilumab responsiveness (56).

A post hoc analysis further confirmed that dupilumab combined with medium-dose ICS achieved significant reductions in FeNO and serum total IgE levels compared with placebo plus high-dose ICS. Median BEC decreased steadily from week 12 and remained stable through week 52 (−130 cells/μL in the dupilumab group *vs.* −70 cells/μL with placebo). Over one year, the addition of dupilumab to medium-dose ICS led to a 74% reduction in severe exacerbations and superior improvements in lung function and asthma control compared with high-dose ICS alone. These findings suggest that dupilumab may enable effective asthma control with lower corticosteroid exposure, potentially reducing steroid-related adverse effects (57).

Transient blood eosinophilia, observed in 4-14% of dupilumab-treated patients compared with < 1% in placebo, is thought to result from inhibited eosinophil migration into tissues rather than increased production or release from the bone marrow (23).

Further analysis by Bacharier *et al.* confirmed that blood eosinophils and FeNO are both valuable predictive and prognostic biomarkers for dupilumab response. The most substantial improvements in exacerbation rates and lung function occurred in patients with elevated levels of both markers, whereas minimal benefit was seen in those with eosinophils < 150 cells/μL and FeNO < 20 ppb (58).

Long-term outcomes from the EXCURSION extension study demonstrated that dupilumab maintains durable efficacy and safety over two years. Children who continued therapy showed sustained improvements in lung function and reduced exacerbation frequency, while those transitioning from

placebo experienced rapid clinical benefits after initiation. The safety profile remained favorable, with mild upper respiratory tract infections and injection-site reactions as the most common adverse events, and no new safety signals emerging over extended follow-up (59).

Tezepelumab

Tezepelumab is a fully human IgG2λ monoclonal antibody approved by both the FDA and the EMA as an add-on maintenance therapy for severe asthma in adults and adolescents aged 12 years and older. It is indicated for patients whose asthma remains uncontrolled despite high-dose ICS combined with at least one additional controller medication, irrespective of BEC (60, 61). According to the NICE guidelines, eligibility includes patients with ≥ 3 exacerbations requiring OCS in the previous year or those requiring maintenance OCS (62).

The recommended dose is 210 mg administered subcutaneously every four weeks (23).

By neutralizing TSLP, tezepelumab inhibits the initiation of both T2 and non-T2 inflammatory pathways, offering potential benefits for patients with low biomarker levels or poor responsiveness to corticosteroids. This upstream mechanism distinguishes tezepelumab from other biologics that target downstream cytokines, making it a promising option for patients across a broad spectrum of asthma endotypes (24).

Mechanistic studies have provided insights into tezepelumab's effect on airway inflammation. Sverrild *et al.* investigated the impact of TSLP inhibition on antiviral responses and airway epithelial inflammation in adult patients with uncontrolled asthma. Bronchoalveolar lavage fluid and bronchial epithelial cells collected before and after 12 weeks of tezepelumab or placebo were exposed to viral mimics (poly(I:C)) or Rhinovirus. Tezepelumab treatment reduced IL-33 expression and the production of T2 cytokines (IL-4, IL-13, IL-17A) in response to poly(I:C), without affecting antiviral markers (IFN-β, IFN-λ) or viral load. These findings indicate that TSLP blockade can attenuate airway epithelial inflammation while preserving antiviral defenses (63).

The NAVIGATOR Phase III trial confirmed the clinical efficacy of tezepelumab in adults and adolescents, demonstrating a 56% reduction in the annual rate of asthma exacerbations, with reductions up to 71% in patients with eosinophil counts ≥ 300 cells/μL. Notably, tezepelumab also

showed efficacy in patients with low eosinophil counts (< 150 cells/μL) and low FeNO values, populations that typically respond poorly to conventional T2-targeted therapies. The treatment consistently improved lung function, asthma control, and health-related QoL (64, 65).

In younger children aged 6 to under 12 years, the ongoing Phase III trial (NCT06023589) is evaluating the safety, efficacy, and pharmacokinetics of tezepelumab in severe, uncontrolled asthma. Data from this study are expected to provide critical evidence for extending pediatric approvals and supporting its clinical use in this age group (66).

Table 1 summarizes the main characteristics of biologics approved in children and adolescents with severe asthma.

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Emerging biologic therapies are expanding the horizons of precision medicine in severe pediatric asthma. Anti–IL-33 monoclonal antibodies, including itepekimab and etokimab, target the IL-33/ST2 signaling pathway, which is critical for activation of ILC2s and eosinophilic inflammation. Early trials in adults have demonstrated reductions in exacerbation frequency and symptom severity, highlighting the potential of IL-33 blockade for children with severe asthma. Depemokimab, a long-acting anti–IL-5 monoclonal antibody with an extended dosing interval, has recently demonstrated promising efficacy in reducing exacerbations in eosinophilic asthma and may further expand future treatment options, pending pediatric evaluation. Similarly, tralokinumab, an IL-13–specific antibody, has shown clinical efficacy in atopic dermatitis and is under investigation for asthma phenotypes predominantly driven by IL-13. Additional investigational agents are focusing on pathways involving IL-1 family cytokines, TSLP receptors, IL-4/IL-13, and IL-17, reflecting the complex interplay of Th2 and non-Th2 inflammatory responses in severe asthma (67-69). The clinical integration of these therapies will depend on the results of ongoing pediatric trials, validation of epithelial and immunologic biomarkers, and development of individualized treatment strategies informed by molecular and cellular profiling.

Ongoing monitoring remains a cornerstone of biologic therapy. Follow-up should include symptom assessment, lung function testing, QoL questionnaires, and periodic biomarker reassessment to

evaluate treatment efficacy and guide long-term decisions. The optimal duration of therapy and criteria for tapering or discontinuation are not yet clearly established in pediatric populations (70).

Real-world evidence provides valuable insights. The Severe Pediatric Asthma Collaborative in Europe (SPACE) study, which followed 250 European children with severe asthma treated with biologics, demonstrated that most achieved good disease control, though approximately one-third maintained partial or poor control. The SPACE network aims to refine recommendations regarding biologic continuation, switching, or discontinuation, promoting a more personalized therapeutic approach (71).

Despite their clinical benefits, biologic therapies pose economic and practical challenges. High treatment costs and variability in insurance coverage may limit access, necessitating careful cost–benefit considerations that weigh reductions in exacerbations, hospitalizations, and corticosteroid exposure against overall healthcare expenditure (72).

Another critical challenge involves immunogenicity, as biologic agents can elicit anti-drug antibodies (ADAs) that may compromise therapeutic outcomes. Among these, neutralizing antibodies represent a clinically significant subset that directly interferes with the biologic's mechanism of action by preventing its binding to the target antigen (73).

The immunogenicity of biologics is determined by a complex interplay of patient-specific and drug-specific factors. Patient-related factors include genetic susceptibility, co-treatments and disease state. Drug-related factors encompass dose, route and frequency of administration, formulation components, post-translational modifications, molecular origin, and the specific target of the monoclonal antibody. ADAs may be generated via T cell-dependent or T cell-independent pathways. In the T cell-dependent pathway, biologics are internalized by antigen-presenting cells, processed, and presented to T cells via major histocompatibility complex (MHC) class II molecules. Depending on the local cytokine milieu, Th cells differentiate into distinct subsets—primarily Th1 or Th2—which, through interaction with B cells, promote the proliferation of plasma cells (PCs) that secrete ADAs. Th2 responses have been associated with increased production of IgG4 isotype ADAs, whereas Th1 responses may favor the generation of IgG1 and IgG2 subclasses. Conversely, in the T cell-independent pathway, biologics presenting multiple epitopes can crosslink B cell receptors (BCRs),

directly stimulating B cell activation and differentiation into PCs. Aggregates or impurities in biologic formulations can enhance epitope clustering, thereby favoring BCR crosslinking and T cell-independent ADAs production (74).

This immunogenic response can interfere with treatment through several mechanisms. ADAs may neutralize the biologic by binding to its active site, thereby preventing interaction with its target. They can also accelerate drug clearance by promoting Fc-mediated uptake through the reticuloendothelial system. Additionally, the formation of immune complexes between the biologic and ADAs can provoke hypersensitivity reactions, including infusion-related responses, serum sickness, or anaphylaxis (75).

Given the increasing use of biologics in the management of severe pediatric asthma, there is a critical need to elucidate the mechanisms, prevalence, and clinical implications of ADAs development. Improved knowledge in this area will facilitate the identification of predictive biomarkers for early ADAs detection, support the implementation of personalized treatment strategies, and ultimately enhance long-term therapeutic efficacy and safety.

CONCLUSIONS

When children with severe asthma remain symptomatic despite optimal therapy, treatment with biologics should be considered. These targeted agents require precise identification of the patient's inflammatory endotype to ensure appropriate selection. Choice of therapy depends on age, biomarker profile, comorbidities, and psychosocial context. Although recent trials have advanced biomarker-based stratification, greater inclusion of diverse pediatric phenotypes is needed. A standardized definition of remission in childhood asthma is still lacking, and prospective evidence confirming biologic-induced remission is absent. Establishing remission as a therapeutic goal could promote earlier, individualized interventions and long-term disease modification. Key priorities include defining optimal treatment duration, discontinuation criteria, and long-term safety. Global inequities in access persist due to variable regulatory and reimbursement frameworks. Multidisciplinary management and updated guidelines integrating precision tools, shared decision-

making, and real-world monitoring are essential to optimize biologic therapy and ensure equitable, evidence-based care for all children with severe asthma.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

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Data falsification and fabrication

All data reported are accurate and authentic.

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Table 1. *Main characteristics of biologics currently approved for severe pediatric asthma.*

Biologic	Target	Mechanism and key immunologic effects	Dosing and mode of administration	FDA authorization	EMA authorization
Omalizumab	IgE (Cε3 domain)	Binds free IgE; ↓ FcεRI/FcεRII engagement; ↓ FcεRI expression; ↓ mast cell/basophil activation; ↓ IgE synthesis; ↑ pDCs TLR function and IFN-α; ↓ IL-33, IL-6, IL-1β, TNF-α	Administered subcutaneously every 2–4 weeks; dose determined by baseline total serum IgE levels and body weight according to validated dosing tables	≥ 6 years	≥ 6 years
Mepolizumab	IL-5	Neutralizes IL-5; ↓ eosinophil maturation, recruitment, survival, activation; ↓ eosinophilic airway inflammation; restores IFN-γ/IL-5 balance; potential antiviral immunomodulation	40 mg subcutaneously every 4 weeks in children aged 6–11 years; 100 mg subcutaneously every 4 weeks in patients ≥12 years	≥ 6 years	≥ 6 years

Benralizumab	IL-5Rα	Binds IL-5Rα; ADCC; near-complete eosinophil and basophil depletion; ↓ eosinophilic inflammation	Subcutaneous administration; in children aged 6–11 years, 30 mg if body weight ≥35 kg and 10 mg if <35 kg (FDA-approved regimen)	≥ 6 years	≥ 18 years
Dupilumab	IL-4Rα	Blocks IL-4Rα; inhibits IL-4/IL-13 signaling; ↓ T2 inflammation; ↓ IgE class switching; ↓ eosinophilic inflammation; ↓ mucus hypersecretion; ↓ bronchial hyperresponsiveness; ↓ airway remodeling; ↓ FeNO; Th2→Th1 immune shift; ↑ IFN-γ	Subcutaneous administration; dosing based on age, body weight, and concomitant OCS use	≥ 6 years	≥ 6 years

Tezepelumab	TSLP	Neutralizes TSLP; blocks upstream alarmin signaling; ↓ T2 and non-T2 inflammation; ↓ IL-33, IL-4, IL-13, IL-17A; preserves IFN-β/IFN-λ antiviral responses; efficacy across biomarker-defined endotypes	210 mg administered subcutaneously every 4 weeks	≥ 12 years	≥ 12 years

ADCC: antibody-dependent cellular cytotoxicity; EMA: European Medicines Agency; FDA: Food and Drug Administration; FeNO: fractional exhaled nitric oxide; IFN: interferon; IgE: immunoglobulin E; IL: interleukin; IL-4Rα: IL-4 receptor α-subunit; IL-5Rα: IL-5 receptor α-subunit; OCS: oral corticosteroid; pDCs: plasmacytoid dendritic cells; T2: type 2; Th: T helper; TLR: toll-like receptor; TNF-α: tumor necrosis factor-α; TSLP: thymic stromal lymphopoietin