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Biologic Therapies Targeting Type-2 Inflammation in Pediatric Chronic Rhinosinusitis: Evidence, Extrapolation From Adults, and a Pediatric Research Agenda

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SUMMARY

Pediatric chronic rhinosinusitis (CRS), particularly when complicated by nasal polyps (CRSwNP), spans a spectrum of age-dependent endotypes that challenge one-size-fits-all management. Emerging evidence – integrating pathology, multi-omic profiling, and real-world cohorts – indicates that younger children commonly exhibit non-type-2 (non-T2) inflammation driven by adenoidal disease and biofilm ecology, whereas adolescents increasingly manifest T2-high signatures that mirror adult CRSwNP. Within this context, biologic therapies targeting T2 pathways (anti-IL-4Rα, anti-IL-5/IL-5Rα, anti-IgE, anti-TSLP) have demonstrated multidomain benefits in adults and growing pediatric applicability, improving nasal polyp burden, congestion, olfaction, and steroid/surgery use when standard care is insufficient. Safety profiles across pediatric experience in related T2 diseases are generally favorable, with predictable and manageable adverse events; nonetheless, child-specific long-term data remain limited. This review synthesizes the pathophysiology and endotypes in childhood and adolescence, maps biomarker-guided selection, and summarizes evolving regulatory landscapes. Persistent gaps include the scarcity of randomized pediatric trials, incomplete validation of biomarkers and response criteria for children, and the need for cost-effectiveness analyses that reflect school participation and caregiver burden. Overall, biologics represent a meaningful advance for T2-high adolescent CRSwNP, enabling targeted, generally safe, steroid- and surgery-sparing strategies, while underscoring the imperative for dedicated pediatric trials, standardized endpoints, and robust pharmacovigilance to realize their full potential in comprehensive care.

KEYWORDS: biologic therapy, pediatric chronic rhinosinusitis, nasal polyps, type-2 inflammation, dupilumab, mepolizumab, benralizumab, omalizumab, tezepelumab, biomarker, research agenda

1. INTRODUCTION

Pediatric chronic rhinosinusitis (PCRS) is defined as persistent inflammation of the sinonasal mucosa lasting for 12 weeks or more and is characterized by nasal obstruction, rhinorrhea, chronic cough, and reduced quality of life [1,2]. With an estimated prevalence of 2-4% in children [3] and a significant impact on health, daily functioning, and healthcare costs – both direct and indirect, including school absenteeism and parental work loss [2,3] – PCRS has become an important focus of research. The nasal polyp phenotype (CRSwNP) is rare in

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children (~0.1%) [4] significantly affecting their quality of life. Chronic rhinosinusitis (CRS, but it should prompt evaluation for underlying systemic conditions such as cystic fibrosis, primary ciliary dyskinesia, and immunodeficiencies [5].

Conceptually, PCRS arises from the interaction between host immune responses, anatomical obstruction, and microbial factors [6,7]. Adenoidal hypertrophy functions as both a mechanical barrier and a bacterial reservoir, thereby worsening mucociliary dysfunction and maintaining inflammation. This framework highlights the importance of integrated diagnostic and therapeutic strategies that target both the inflammatory environment and structural factors contributing to disease persistence [7,10]. Understanding these relationships is vital for personalizing interventions and enhancing both management of symptoms and quality of life.

Despite expanding research, management remains challenging due to an incomplete understanding of the underlying causes and heterogeneous treatment responses. PCRS encompasses multiple phenotypes influenced by adenoidal hypertrophy, allergic rhinitis, immunodeficiencies, and microbial dysbiosis [10-12]. Current guidelines emphasize medical therapy (nasal hygiene, intranasal corticosteroids, antibiotics). Meanwhile, the timing and role of surgery – such as adenoidectomy, balloon sinuplasty, and functional endoscopic sinus surgery (FESS) – are still debated [1,13,14]. Ongoing discussions include whether adenoidectomy alone is effective versus combined approaches and the effects of new biologic and immunomodulatory treatments [15-17]. Limited high-quality evidence leads to inconsistent practices and potentially less effective outcomes [18,19].

Over the past decade, advances in the immunopathology of CRSwNP have identified type-2 (T2) inflammation – driven by IL-4, IL-5, and IL-13 – as a key pathological mechanism [20,21], paving the way for targeted biologics (dupilumab, omalizumab, mepolizumab). These agents are effective in adults and are increasingly being considered for pediatric use [22,23]. While biologics have transformed the treatment of severe adult CRSwNP [24,25], evidence in children remains limited, requiring a cautious, personalized approach based on rational extrapolation and careful patient selection.

Pediatric-adult differences are significant: an evolving immune system, biofilm formation, and microbial dysbiosis contribute to pediatric pathobiology [10,26,27]. PCRS differs from adult CRS in epidemiology, anatomy, and immunopathogenesis [28]; limited sinus pneumatization, the central role of adenoids as bacterial reservoirs, and the predominance of non-T2 patterns in early stages shape the clinical presentation [8,29]. Adenoidal hypertrophy, mucociliary dysfunction, and recurrent respiratory infections are key drivers of non-polypoid disease [9].

Conversely, prepubertal and adolescent CRSwNP more often show a T2 endotype with eosinophilic infiltration and activation of IL-4, IL-5, and IL-13, paralleling adult disease [30,31]. This cluster is associated with allergic multimorbidity (asthma, allergic rhinitis, atopic dermatitis), immunodeficiencies, and respiratory comorbidities (e.g., cystic fibrosis), leading to more severe phenotypes that are often resistant to standard therapy [12,19,32,33].

A clear knowledge gap remains: only a few studies and compassionate-use case reports assess the use of biologics in children [34-36], and uncertainties persist regarding safety, effectiveness, cost-effectiveness, and predictive biomarkers [37-39]. These gaps may limit the availability of evidence-based guidance and contribute to disease burden [40].

This review combines T2 pathophysiology in pediatric CRSwNP with the mechanisms of monoclonal antibodies targeting IL-4, IL-5, IL-13, and IgE, along with their clinical applications. Its goal is to summarize current evidence on monoclonal antibodies and biologic therapies in pediatric chronic rhinosinusitis, emphasizing efficacy, safety, and clinical relevance to inform practice and guide future research priorities.

2. PATHOPHYSIOLOGY AND ENDOTYPES IN CHILDREN AND ADOLESCENTS

Over the past decade, understanding of the immunopathogenesis of pediatric chronic rhinosinusitis (PCRS), with or without nasal polyps (CRSwNP), has significantly evolved. A condition once mainly viewed through infectious or mechanical perspectives is now recognized as a range of immuno-inflammatory endotypes that differ based on age, anatomical location, and the presence of multiple health issues. Notably, an adolescent subgroup shows type 2 (T2) – dominant inflammation similar to that in adult CRSwNP, whereas preschool and school-age children more often display non-T2 patterns. These endotypic differences are not merely taxonomic; they predict disease progression, treatment response, and prognosis, and therefore inform selection of advanced therapies and research design [28,41,42]. The main differences between pediatric non-T2 and T2 endotypes are summarized in Table I.

In younger children, inflammation is usually non-T2 and marked by neutrophils, macrophages, and T-cell-predominant infiltrates with overexpression of IL-6, IL-8, and TNF-α, often in the context of anatomical crowding and adenoidal disease. Persistent bacterial biofilms anchored to the adenoids serve as a focus for recurrent upper-airway infections and mucosal irritation, maintaining a cycle of mucus stasis and epithelial stress that perpetuates symptoms and suboptimal responses to purely anti-inflammatory treatments [43-45]. Ultrastructural and culture-independent studies consistently demonstrate mature biofilms on adenoidal tissue in the vast majority of PCRS – often cited as 85-95% – and these correlate with disease severity and the need for intervention when medical therapy fails [46-48]. Histopathology in this age window generally shows substantial tissue eosinophilia, while immunophenotyping reveals dense clusters of neutrophils and myeloid dendritic cells, aligning with the clinical success seen with adenoidal surgery, nasal hygiene, and targeted antimicrobial treatments when carefully chosen [46].

Beginning in preadolescence, a progressive endotypic shift toward T2 dominance becomes increasingly evident. The mucosa develops

TABLE I. Comparison of pediatric endotypes in chronic rhinosinusitis. This Table summarizes the principal differences between the two predominant inflammatory endotypes in childhood: the non-T2 endotype – typical of early childhood and primarily driven by mechanical – infectious factors – and the T2 endotype – more frequent in adolescents and characterized by an adult-like type-2 immune response. Differences span age at presentation, immunologic/cytokine profile, associated biomarkers, comorbidities, therapeutic response, and prognosis. These distinctions carry significant clinical implications, enabling a personalized treatment approach: in younger children, priority lies in controlling mechanical-infectious drivers (adenoids, biofilm), whereas in T2-high adolescents, escalation to targeted therapies – including off-label biologics – may be appropriate based on phenotype and endotype.

Dimension	Non-T2 endotype (predominant in < 12 years)	T2 endotype (more frequent ≥ 12-13 years / adolescents)
Typical age	Preschool/school-age	Pre-adolescents and adolescents
Main drivers	Mechanical factors (adenoidal hypertrophy), bacterial biofilms, recurrent upper-airway infections; mucociliary dysfunction	Aero-/indoor allergens, epithelial barrier dysfunction, alarmins (TSLP/IL-33/IL-25), Th2/ILC2 immune amplification
Histopathology	Neutrophil and macrophage infiltrates; absent/mild eosinophilia; mucous gland hyperplasia associated with adenoidal biofilm	Marked eosinophilic infiltrate; mucous gland hyperplasia; stromal edema; fibroblast-mediated remodeling; B-cell plasma cells and local IgE
Cytokines/axes	IL-6/IL-8/TNF-α; variable T1/T3 signals	IL-4/IL-13 (STAT6), IL-5/IL-5R, TSLP/IL-33/IL-25; ILC2 activation
Useful biomarkers	Middle-meatus swab/pathogen workup; adenoidal imaging; PCR/cultures as needed	Peripheral eosinophils, total/specific IgE, FeNO, local IgE (in reference centers); T2-high transcriptomic/histologic profiles
Associated comorbidities	Recurrent otitis media/OME; OSAS; recurrent infections	Allergic asthma, allergic rhinitis, atopic dermatitis; anosmia/hyposmia
Endoscopy/imaging	Hypertrophic adenoids; thick secretions; biofilm signs	Nasal polyps (when present), diffuse polypoid edema; high endoscopic scores
Response to standard therapy	Good response to saline irrigations + INCS, targeted antibiotics, adenoidectomy	Often partial response to INCS; recurrences after surgery; high symptom burden
Role of surgery	Adenoidectomy is the mainstay after medical failure; FESS only in selected cases	FESS after medical optimization; increased recurrence risk in eCRS
Candidacy for biologics (off-label)	Limited; exceptional indications	High in refractory T2-high cases (dupilumab, anti-IL-5/IL-5R, omalizumab; TSLP evolving)
Monitoring objectives	Reduce infections; QoL; need for antibiotics/surgery; follow-up endoscopy	NPS, SNOT-22, smell testing, reduction in systemic steroids/surgery; T2 markers (eos/IgE/FeNO)
Prognosis	Good with mechanical-infectious management (adenoid-first)	Higher risk of recurrence and clinical burden; biomarker-guided strategy required
Research priorities	Microbiome/biofilm-targeted care; algorithms for surgical selection	Pediatric RCTs on biologics; validation of predictive biomarkers; cost-effectiveness

INCS: intranasal corticosteroids; OME: otitis media with effusion; OSAS: obstructive sleep apnea syndrome; FESS: functional endoscopic sinus surgery; QoL: quality of life; NPS: Nasal Polyp Score; FeNO: fractional exhaled nitric oxide; eCRS: eosinophilic chronic rhinosinusitis; eos: eosinophils.

perivascular and stromal eosinophilic infiltrates, with activation of the IL-4/IL-13/IL-5 axis, expansion of ILC2 and Th2 lineages, rising local IgE, and signs of epithelial barrier dysfunction accompanied by subepithelial fibroblast activation [49-52]. This transition is intensified by allergic multimorbidity – such as asthma, allergic rhinitis, and atopic dermatitis – and by ongoing environmental allergen exposure, which together expand and stabilize the upper-airway T2 program and its downstream effector pathways [52-54]. In this context, multi-omic studies conducted in older children and adolescents reveal a molecular fingerprint of T2-high CRSwNP, including upregulation of IL-4/IL-13 transcripts and activation of the JAK-STAT6 pathway, overexpression of IL-5/IL-5Rα, alongside tissue and blood eosinophilia, increased ILC2 density, and enrichment of IgE-secreting plasmablasts within the polyp strom [41,55-57]. Significantly, these tissue programs correlate with clinical severity indices – NPS and SNOT-22 – and with refractoriness to standard intranasal

corticosteroids and saline irrigation, providing a biological rationale for targeted therapy using biologics.

A clinically important related aspect is the eosinophilic CRS (eCRS) endotype, which indicates higher symptom burden, poorer surgical outcomes, and a greater risk of recurrence, often requiring multiple revisions after endoscopic surgery [58-60]. In a study carried out in 2024 involving a multicenter cohort of 211 adolescents with CRSwNP, a threshold of ≥ 50 eosinophils per high-power field in polyp tissue independently predicted 12-month postoperative recurrence, even after adjusting for baseline disease severity and comorbid asthma [59]. Additional data have linked increased IL-5 expression and local IgE to higher re-operation rates and persistent anosmia, highlighting the strong connection between tissue-level immune response and long-term surgical outcomes [60-62].

Beyond canonical Th2 cytokines, epithelial alarmins (TSLP, IL-33, and IL-25) act as upstream amplifiers that prime dendritic cells and ILC2 circuits, enhance IL-5/IL-13 production, and coordinate eosinophilopoiesis and recruitment to polypoid mucosa [50,56,63]. Meanwhile, polyp-derived fibroblasts develop a secretory, matrix-remodeling phenotype marked by TGF-β, VEGF, IL-6, and CXCL8 output, collectively fostering edema, glandular hyperplasia, and extracellular matrix deposition. This stromal program stabilizes the polyp architecture and contributes to treatment resistance, especially when inflammatory triggers persist uninterrupted [45,64]. These epithelial-stromal feedback loops help explain why some adolescents with T2-high disease remain poorly controlled despite optimal medical therapy and why upstream blockade (e.g., TSLP inhibition) is being investigated alongside downstream IL-5/IL-4Rα targeting.

Converging evidence also points to a pivotal crosstalk between the microbiome and the immune system. Dysbiosis – including depletion of commensal genera such as *Corynebacterium* and *Dolosigranulum* – associates with heightened T2 activation and epithelial vulnerability, potentially facilitating allergen ingress and barrier breakdown [65,66]. In practical terms, these shifts may mark the inflection point at which an infection-predominant CRS evolves into a chronic inflammatory disease with autonomous tissue circuits and diminished responsiveness to antibiotics alone.

The clinical implications of these endotypic differences are immediate. In younger, non-T2-dominant children, thorough nasal hygiene, strategic adenoidal management, and biofilm control remain key practices and are often sufficient to restore mucosal homeostasis. In contrast, in T2-high adolescents with multimorbidity, traditional treatments are often inadequate; in such cases, escalating to carefully selected off-label biologics – aligned with the endotype-biomarker profile – becomes a logical step, ideally within centers experienced in pediatric airway immunology [33,67,68]. Current EUFOREA/EPOS 2024 consensus statements and pediatric reviews agree on this endotype-driven strategy, proposing selection and follow-up criteria, while explicitly calling for dedicated pediatric trials and standardized endpoints to validate these methods prospectively [33-35].

3. STANDARD THERAPY IN CHILDREN

Management of PCRS follows a stepwise approach that prioritizes non-invasive treatments, rigorous control of comorbidities, and selective surgery in experienced pediatric centers. A practical stepwise approach to pediatric CRS management is outlined in Table II. First-line therapy includes high-volume (when tolerated) isotonic or hypotonic saline irrigations and intranasal corticosteroids (INCS), which have a favorable risk-benefit profile and are well accepted. A pediatric randomized clinical trial (RCT) showed significant improvements in quality of life (SN-5) and sinonasal microbiome diversity, supporting INCS as a cornerstone of PCRS; adverse events were mostly mild and transient [69]. Subsequent studies in 2024-2025 and reviews confirm the efficacy and safety of INCS in children (including FDA-approved sprays, new aerosolized/NAB delivery, and budesonide irrigations in specialist settings), with low systemic bioavailability and minimal risk to growth and the HPA axis at standard doses [70].

Adherence and technique are as crucial as the medication itself: family education, age-appropriate devices, and regular rinses improve effectiveness; common obstacles include poor flow tolerance, improper technique, and the perception of a "chronic medicine." Educational interventions and structured follow-up enhance adherence and outcomes [71]. During exacerbations or in phenotypes with allergic overlap, optimizing rhinosinus hygiene (saline), INCS, and treating allergic rhinitis (antihistamines/antileukotrienes for AR, not for CRS) reduces inappropriate antibiotic use [33].

Long-term low-dose macrolides as immunomodulators remain insufficiently defined in pediatric patients and are not routinely recommended (evidence based mainly on adult data [33].

If, after 12 or more weeks of optimized medical therapy, the response remains inadequate, nasal endoscopy and multidisciplinary assessment guide the next steps. In children under 12 years old, adenoidectomy is the primary surgical option, providing symptomatic relief in most cases; however, benefits are less noticeable in children with significant respiratory comorbidities (such as moderate to severe asthma) or pansinusitis [72].

Data from 2022-2024 indicate that adenoidectomy can reshape the nasal microbiota and reduce persistent inflammation. Outcome reviews report success rates of approximately 50-75%, with variability influenced by age, phenotype, and associated condition [73].

Endoscopic sinus surgery (FESS/PESS) is reserved for selected cases after failure of adenoidectomy and medical therapy, or in complicated or extensive disease (e.g., severe adolescent polyposis). Recent series and reviews report success rates and favorable safety in children, particularly when performed by experts, although the risk of recurrence is higher in T2/eosinophilic phenotypes and in T2 multimorbidities [74].

The role of balloon sinuplasty and balloon ostial dilation remains uncertain: reviews published in 2024-2025 mention modest benefits, higher costs, and limited prospective evidence in children; multiple payer policies consider it no better than standard strategies in pediatric PCRS. Use should be evaluated case by case or in hybrid or salvage situations, rather than as a first-line treatment [75].

TABLE II. Stepwise pediatric care pathway for chronic rhinosinusitis (with/without nasal polyps). The Table outlines a pragmatic, endotype-aware sequence from universal measures (education and high-volume saline irrigations) to INCS, comorbidity optimization, culture-guided antibiotics, and structured endoscopic reassessment, followed – when indicated – by adenoid-first surgery in younger children and selective FESS in refractory disease. In adolescents with T2-high CRSwNP, biomarker-based endotyping (eosinophils, total/specific and, where feasible, local IgE; FeNO) supports escalation to targeted biologics within multidisciplinary programs. Response is evaluated at 16-24 weeks using NPS, SNOT-22, olfactory testing, steroid/surgery sparing, and safety monitoring, with predefined criteria for continuation or switch. Clinical caveats specific to pediatrics include age-appropriate devices and technique, careful documentation of adherence, and longitudinal tracking of growth and pubertal development.

Step	Intervention (what)	When	How	Response indicators	Pediatric notes
1	Education + nasal hygiene	All patients at diagnosis	Saline irrigations (isotonic or hypotonic), preferably high-volume if tolerated; correct technique taught to parent/child	Symptom frequency; SN-5/CF-QoL; reduction of secretions/endoscopic findings	Adherence is the main driver of efficacy; adapt the device to patient age
2	Intranasal corticosteroids (INCS)	After 2-4 weeks of proper hygiene if symptoms persist	Second-generation sprays (mometasone/fluticasone) at standard dose; 8-12 weeks; check technique at every visit	SN-5/SNOT-22 (adolescent), congestion, endoscopy	Low systemic bioavailability; usually mild AEs; re-assess technique/adherence
3	Optimization of comorbidities	In parallel with steps 1-2	Allergic rhinitis (topical/oral antihistamines; environmental control), asthma (per GINA); manage reflux/OSA if present	AR/asthma control; FeNO (if available); sleep quality	T2 multimorbidity (asthma/AR/AD) impacts severity and recurrence
4	Targeted antibiotic (if indicated)	Suspected bacterial superinfection, persistent purulent discharge, fever, clinical worsening	Short course per local guidance and antibiogram; avoid routine long-term low-dose macrolides	Reduction of discharge, pain, fever; endoscopy	Avoid overuse; consider middle-meatus swab/endoscopic sampling
5	Endoscopic assessment	After ≥ 12 weeks of well-conducted therapy, or earlier if red flags	Office nasal endoscopy; semi-quantitative scoring; document technique and adherence	Endoscopic score; video/photos for follow-up	Cornerstone tool for surgical indications and monitoring
6	Adenoidectomy	< 12 years with adenoidal hypertrophy/biofilm or poor medical response	"Adenoid-first" surgery by experienced teams; structured parent counselling	Symptom improvement; fewer exacerbations; reduced secretions	Expected success ~50-75% (variable); lower if pansinusitis/comorbidities
7	Selective FESS	Failure of adenoidectomy + optimized therapy; extensive disease; complications; adolescent CRSwNP	Pediatric-center FESS; post-op protocol: saline + INCS	SNOT-22 (adolescent); NPS (if polyps); olfaction; need for re-intervention	Recurrence more likely in T2/eosinophilic phenotype; close follow-up
8	T2 endotyping (adolescent)	Severe CRSwNP; post-FESS recurrence; T2 multimorbidity	Peripheral eosinophils; total/specific IgE; FeNO; (if feasible) local IgE/biopsy	Defined T2-high profile	Guides targeted-therapy choices and monitoring strategy
9	Biologic therapies (off-label in CRS)	T2-high adolescent refractory after steps 1-7; on-label for asthma/AD	Target-driven choice: anti-IL-4Rα (dupilumab), anti-IL-5/IL-5R (mepo/benra), anti-IgE (omalizumab); informed consent; predefined outcome plan	NPS; SNOT-22; olfaction; reduction in systemic steroids/surgery; safety	Multidisciplinary care; prospective registries; reassess at 16-24 weeks

SN-5: Sinonasal 5; CF-QoL: Cystic Fibrosis Quality of Life (or center-specific QoL tool); INCS: intranasal corticosteroids; AEs: adverse events; AR: allergic rhinitis; GINA: Global Initiative for Asthma; OSA: obstructive sleep apnea; AD: atopic dermatitis; FESS: functional endoscopic sinus surgery; NPS: Nasal Polyp Score; FeNO: fractional exhaled nitric oxide; mepo/benra: mepolizumab/benralizumab.

A key aspect of standard care is identifying comorbidities and warning signs: adolescent CRSwNP, suspected cystic fibrosis/PCD, immunodeficiencies, or moderate-to-severe asthma require dedicated assessments and collaborative approaches involving allergy, pulmonology, and genetics. In T2-high phenotypes, escalation to biologics, although off-label for CRS in children but approved for asthma and atopic dermatitis, should occur only after optimizing standard treatment and considering surgery, with structured monitoring (using NPS, SNOT-22, and olfaction tests) and informed consent. The 2024 position statements emphasize a stepwise approach and the importance of pediatric-specific criteria, clearly differentiating adenoid-driven PCRS from T2-driven adolescent disease [33].

Imaging with low-dose CT is only recommended when it would influence management decisions, such as before surgery, in cases of complications, or when the disease does not respond to treatment, to minimize radiation exposure. Nasal endoscopy remains essential for diagnosis, follow-up, and guiding treatment. After surgery, saline irrigation and INCS are advised to prevent synechiae and recurrence and promote healing [74].

In summary, standard pediatric care includes saline with INCS, correcting mechanical factors (adenoids), and selective surgery; adherence and technique influence effectiveness, while endotyping, especially in T2-high adolescents, guides decisions about advanced therapies [69,76,77].

4. BIOLOGICS IN PEDIATRIC CRSWNP: ADULT EVIDENCE AND PEDIATRIC IMPLICATIONS

The use of biologics in pediatric chronic rhinosinusitis with nasal polyps (CRSwNP) is driven by the need to provide a practical option for T2-high cases who do not respond to optimized standard care (saline irrigations, intranasal corticosteroids) and, in some cases, surgery. This approach considers anatomical and physiologic differences between children and adults, as well as the rarity of CRSwNP in childhood. Without randomized controlled trials in pediatric patients, treatment decisions should be based on a solid immunopathogenic rationale (IL-4/IL-13, IL-5/IL-5R, IgE, and the epithelial alarmin TSLP), proven efficacy in adult RCTs, and pediatric regulatory approvals from other T2 conditions (such as asthma and atopic dermatitis) in carefully selected adolescents. The choice of therapy should therefore be guided by endotype, combined with a predefined multidomain monitoring plan (NPS, SNOT-22, olfaction, steroid/surgery avoidance), and by clear stop or switch rules at 24-52 weeks, within a multidisciplinary pathway and with informed consent for off-label use. This careful, biomarker-driven approach aims to responsibly address the pediatric evidence gap, pending dedicated prospective studies and real-world registries to consolidate effectiveness, safety, and cost-effectiveness. An overview of key biologic therapies for CRSwNP, including adult evidence, pediatric anchors, and 2025 regulatory status, is presented in Table III.

4.1 Dupilumab (anti-IL-4Rα): dual blockade of the IL-4/IL-13 axis and downstream STAT6

Target and receptors

Dupilumab is a humanized IgG4 antibody that binds to IL-4Rα, the shared subunit of both type I (IL-4Rα/γc) and type II (IL-4Rα/IL-13Rα1) receptor complexes. By engaging IL-4Rα, dupilumab prevents signaling by IL-4 (via type I and type II receptors) and IL-13 (via the type II receptor), thereby blocking the upstream JAK-STAT6 transcriptional pathway that controls multiple T2-response genes (e.g., eotaxins, periostin, CLCA1, and MUC5AC). This results in decreased eosinophil chemotaxis, inhibition of IgE class-switch, and restoration of epithelial barrier function (including tight junctions and mucociliary differentiation). Clinical and translational studies show rapid functional blockade of receptor signaling in T and B cells and airway epithelium, with early downregulation of STAT6-dependent programming within hours after dosing [78-81].

Relevance to CRSwNP

In T2-high polyp tissue, dupilumab suppresses the IL-13 signature, reduces stromal edema and remodeling (fibroblast/matrix programs), and improves NPS, nasal symptoms, and olfaction, while lowering systemic steroid use and the need for revision surgery in post-marketing real-world cohorts. Its dual-pathway (IL-4/IL-13) blockade explains its broad efficacy in T2 multimorbidity (asthma/dermatitis), making dupilumab an attractive upstream option for adolescents with T2-high CRSwNP [81]. Beyond the pivotal trials, the last 5 years have produced robust real-world and comparative evidence: multicenter European series and practice-based meta-analyses confirm reductions in NPS, and improvements in nasal congestion, SNOT-22, and smell, alongside substantial steroid-sparing and fewer surgical revisions [82-84]. A real-world analysis in 2025 documented rapid, sustained benefit with a safety profile consistent with clinical trials (injection-site reactions, rare conjunctivitis) [82]. Observational data in 2025 also suggest efficacy independent of baseline polyp load, suggesting a broad response spectrum within T2-high disease [85]. Moreover, an indirect comparison and a prospective head-to-head analysis in (2025 suggested clinical advantages over omalizumab in key endpoints (NPS, symptoms), while underscoring the need for pragmatic confirmation and cost-effectiveness evaluation [86].

Pediatric relevance

In Italy/EU and the USA, dupilumab is approved for asthma and atopic dermatitis, providing a regulatory basis for off-label use in adolescent T2-high CRSwNP that is refractory to standard treatment.

TABLE III. Overview of biologic therapies relevant to CRSwNP (adult RCT evidence, pediatric anchors from other T2 indications, 2025 regulatory status in USA/EU-Italy, and pragmatic adolescent use). Adult evidence is used to inform off-label decisions in adolescents with T2-high PCRS/CRSwNP when standard care fails, with structured 16-24-week reassessment (NPS, SNOT-22, olfaction, steroid/surgery sparing) and predefined stop/switch rules. Safety profiles reflect trial and real-world data in CRS or related T2 diseases.

Target	Agent	Mechanism	Adult CRSwNP evidence (key endpoints)	Regulatory status for CRSwNP (2025)	Practical pediatric use (adolescents)	Key safety notes
IL-4Rα (IL-4/IL-13)	**Dupilumab**	Blocks IL-4Rα → inhibits IL-4/IL-13 (STAT6)	Improves NPS, congestion, SNOT-22, olfaction; steroid/surgery sparing; robust real-world confirmation.	US: adults (2019) and **adolescents ≥ 12 y** since 13-Sep-2024; EU/Italy: adults; pediatric CRSwNP not yet labeled.	T2-high with smell loss/multimorbidity; assess at 16-24 wk with NPS/SNOT-22/olfaction.	ISRs, rare conjunctivitis; transient eosinophilia.
IL-5	**Mepolizumab**	Neutralizes IL-5	Phase 3 SYNAPSE: ↓NPS, ↓obstruction; post-hoc: steroid/surgery sparing; benefit clearer when eosinophils higher.	US/EU: **adults** with CRSwNP (2021); pediatric CRSwNP off-label.	Eos-high adolescents, post-FESS relapse; track eosinophils + NPS/SNOT-22.	Headache, ISRs; rare HZ.
IL-5Rα	**Benralizumab**	Afucosylated anti-IL-5Rα → **ADCC** eosinophil depletion	Phase 3 OSTRO: ↓NPS & congestion; rapid blood/tissue eosinophil depletion; mixed secondary endpoints (selection matters).	**Not approved** for CRSwNP (US/EU) as of 2025.	"Hit-hard" in marked eosinophilia; consider *vs.* anti-IL-5 by phenotype and adherence.	ISRs, headache; mild URTIs.
IgE	**Omalizumab**	Binds free IgE → ↓FcεRI signaling; affects local intrapolyp IgE circuit	POLYP-1/-2 era + 2021-25 RWE: ↓NPS, ↓symptoms, ↑QoL; utility even with local IgE.	US/EU: adults for CRSwNP; pediatric CRSwNP off-label.	Consider if strong atopy or suspected local IgE; monitor 16-24 wk.	ISRs, headache; **rare** anaphylaxis (observe early doses).
TSLP (alarmin)	**Tezepelumab**	Neutralizes TSLP (upstream DC/ILC2 priming)	Phase 3 **WAYPOINT**: ↓NPS, ↓congestion, ↓SNOT-22; ↓OCS/surgery; effect across eos/non-eos.	**US approval Oct-2025** for CRSwNP ≥ 12 y; **EU approval 2025** (adults first).	Useful when upstream trigger suspected (mixed/non-eos); assess at 16-24 wk.	Nasopharyngitis, headache, local reactions; no immunosuppression signal.

In expert centers, patient selection may depend on T2 multimorbidity, eosinophilia, IgE/FeNO levels, and olfactory loss, with structured monitoring (NPS, SNOT-22, smell tests) at 16-24 weeks [82-84,86].

Updated regulatory notes (USA/EU)

In the United States, the CRSwNP indication, initially approved for adults in 2019, was extended to adolescents aged 12-17 years on 13

September 2024 as an add-on therapy in inadequately controlled disease. The extension specifies a body-weight threshold of ≥ 40 kg and clarifies that safety and efficacy have not been established in children under 12 years [87,88]. In Europe (and therefore in Italy), dupilumab is indicated in adults as add-on to INCS in severe CRSwNP inadequately controlled by systemic corticosteroids and/or surgery [89,90]; for the pediatric population, EU labels remain tied to other T2 conditions (asthma, atopic dermatitis) with age thresholds that vary by indication, but do not yet include pediatric CRSwNP [91].

4.2 Mepolizumab (anti-IL-5): neutralizing IL-5 to "deflate" eosinophilic biology

Target and IL-5 cascade

Mepolizumab is a humanized IgG1 antibody that binds to and neutralizes IL-5 in the bloodstream, preventing it from engaging IL-5R (IL-5Rα/βc) on eosinophils. Because IL-5 is essential for the maturation, survival, and activation of eosinophils in bone marrow, blood, and tissues, neutralizing it decreases their trafficking and persistence, reducing cationic activity, reactive oxygen species, and granule proteins (MBP, ECP) involved in epithelial damage and olfactory loss in CRSwNP. Since selective IL-5 blockade does not eliminate other T2 cytokines (IL-4/IL-13), the most significant clinical benefit is anticipated in eosinophil-driven phenotypes with higher peripheral eosinophilia [92-94].

Relevance to CRSwNP

Beyond pivotal trials, reviews from 2024-2025 confirm reductions in NPS and congestion, steroid- and surgery-sparing effects, and a favorable safety profile. Since there is IL-5 dependence of polyp tissue in T2-high adolescents, use of mepolizumab is warranted when the clinical goal is to lower eosinophilia and reduce recurrences, especially after post-FESS relapse [92]. The phase-3 SYNAPSE trial in 2021 showed significant improvements in NPS and nasal obstruction in adults with severe, relapsing CRSwNP despite SOC and surgery, with no new safety signals [95]. A post-hoc analysis in 2023 of surgical endpoints demonstrated longer time to surgery and reduced systemic steroid use, outlining a clinically meaningful steroid- and surgery-sparing profile [96]. The effects are more pronounced in eosinophilic phenotypes with higher baseline blood eosinophil levels.

Pediatric relevance

Approved for children aged 6 years and older with refractory eosinophilic asthma, mepolizumab allows cautious extrapolation to adolescent T2-high CRSwNP with significant eosinophilia and failure of SOC/FESS, especially when the goal is to reduce steroids and surgery. Monitoring should include eosinophil counts, NPS/SNOT-22 scores, and adverse event surveillance (headache, local reactions) [95,96].

Updated regulatory notes (USA/EU)

In the USA, the FDA approved mepolizumab for adult CRSwNP on 29 July 2021, making it the first anti-IL-5 therapy approved for this indication [97]. The European regulatory profile was aligned in 2021, with authorization as an add-on to INCS in adults with severe CRSwNP refractory to systemic steroids and/or surgery. In pediatric patients, CRSwNP remains off-label; however, mepolizumab remains on-label for eosinophilic asthma for ≥ 6 years, providing a regulatory "anchor" for carefully documented off-label use in selected adolescents [98].

4.3 Benralizumab (anti-IL-5Rα): rapid eosinophil depletion via "enhanced" antibody-dependent cellular cytotoxicity

Bifront target and ADCC

Benralizumab is an afucosylated IgG1 antibody targeting IL-5Rα on eosinophils and basophils. Afucosylation enhances Fc affinity for FcγRIIIa on NK cells, increasing antibody-dependent cellular cytotoxicity (ADCC): the antibody opsonizes eosinophils (via IL-5Rα), recruits NK cells, and induces granule-mediated apoptosis. This leads to near-complete depletion of eosinophils in blood and tissue, which is faster and more effective than anti-IL-5 agents, directly reducing edema, obstruction, and mucous hyperplasia. Recent PK/PD and biopsy analyses confirm tissue depletion within polyps, supporting a local mechanism of action [99-102].

Relevance to CRSwNP

In T2-high CRSwNP with marked eosinophilia, a "hit-hard" strategy targeting IL-5Rα can rapidly deflate eosinophilic inflammation and yield perceptible gains in congestion and NPS; impacts on patient-reported outcomes (SNOT-22) may vary by endotype and comorbidity burden, justifying careful phenotypic selection when choosing between anti-IL-5 and anti-IL-5R agents [103]. In the OSTRO trial, benralizumab improved NPS and nasal congestion at 40 weeks compared to placebo, with nearly complete blood and tissue eosinophil depletion. Some secondary endpoints (SNOT-22, time to surgery or steroids) showed variable results, emphasizing the importance of patient selection [104,105]. In 2024, PK/PD and histologic studies confirmed rapid, sustained eosinophil depletion within polyp tissue, supporting the local mechanistic rationale [105].

Pediatric relevance

Approved for individuals aged 12 and older (in some countries approved from age 6) for severe eosinophilic asthma, benralizumab can be used off-label for adolescent T2-high CRSwNP with significant eosinophilia, especially after failure of SOC/FESS or rapid post-surgical relapse. Selection between mepolizumab and benralizumab may depend on eosinophil levels and preferences regarding administration and adherence; common adverse events include local reactions, headache, and rare mild respiratory infections [104,105].

Updated regulatory notes (USA/EU)

As of 2025, there is no marketing authorization for CRSwNP in the

USA or the EU/Italy. Phase 3 clinical data (OSTRO) reported favorable effects on NPS and nasal obstruction, although these have not led to an indication for CRSwNP to date [105].

4.4 Omalizumab (anti-IgE): "emptying the IgE reservoir" and retuning FcεRI

Target and IgE network

Omalizumab is a humanized IgG1 that selectively binds free IgE at Cε3, preventing engagement with FcεRI (mast cells, basophils, DCs). By lowering free IgE, omalizumab downregulates FcεRI, reduces degranulation and immediate/late-phase responses, and indirectly modulates the T2 cytokine environment (lower IL-4/IL-5), with downstream effects on B-cell IgE production and eosinophils. Crucially, omalizumab does not bind receptor-bound IgE (no activating cross-linking), underpinning its favorable safety profile. In CRSwNP, beyond systemic atopy, local intrapolyp IgE is relevant and fuels T2 inflammation in the sinonasal mucosa [106,107].

Relevance to CRSwNP

In T2-high CRSwNP with atopy (or suspected local IgE), IgE detoxification and FcεRI downregulation can lower NPS, symptoms, and recurrences. The extensive pediatric experience with asthma and chronic urticaria supports its good tolerability, with rare cases of anaphylaxis and mostly mild local reactions; careful selection based on total/specific IgE, allergic profile, and T2 multimorbidity remains crucial [106]. Although the pivotal POLYP-1/-2 trials date to 2020 (slightly beyond the 5-year window), the past 5 years have produced real-world studies and comparative analyses that confirm its efficacy and safety in severe CRSwNP, with clinical and endoscopic improvements and lower relapse rates [108,109]. Benefits may also apply to subgroups without systemic atopy, likely through local IgE/FcεRI down-regulation; however, patient selection remains crucial (considering allergic history, total/specific IgE, possible local IgE, and the presence of concomitant AD or asthma) [106].

Pediatric relevance

Approved for children aged 6 years and older for allergic asthma and from 12 years for chronic urticaria, omalizumab enables rational off-label use in adolescent T2-high CRSwNP with atopy, especially when aiming to lower exacerbations and symptom burden in T2 multimorbidity. Common adverse events include injection-site reactions and headaches; anaphylaxis is rare (initial observation recommended) [109].

Updated regulatory notes (USA/EU)

In the United States, omalizumab is indicated for adults aged ≥ 18 years (2024 extension). In July 2025, the FDA approved the first omalizumab biosimilar [110]. In Europe, the European Commission approved omalizumab for CRSwNP in adults on 6 August 2020 (add-on to INCS), the first EU anti-IgE authorization for this disease; Italy follows the EMA route for national labeling [111]. In CRSwNP pediatric patients, it remains off-label.

4.5 Tezepelumab (anti-TSLP): switching off the epithelial "starter" alarmin upstream of Th2/ILC2

TSLP and barrier immunity

TSLP is an epithelial alarmin released in response to allergens, infections, and pollutants; it binds a high-affinity TSLPR/IL-7Rα heterodimer, activating dendritic cells, mast cells, eosinophils, basophils, and ILC2, and promoting Th2 polarization (via OX40L/IL-4/IL-13/IL-5). Tezepelumab (human IgG2λ) neutralizes TSLP and prevents activation of the TSLPR-IL-7Rα complex, reducing inflammation upstream and possibly beyond eosinophilia (effects in T2-low/"non-eos" phenotypes). This upstream targeting explains its broad benefits on NPS, congestion, SNOT-22, and reductions in steroid use and surgery reported in adult CRSwNP, with a safety profile consistent with severe asthma [112-115].

Relevance to CRSwNP

TSLP inhibition is advantageous in adolescence, where multiple epithelial triggers (allergens, viral exposures, pollutants) and T2 multimorbidity frequently coexist; by targeting epithelial-innate priming, tezepelumab may lower steroid dependence and offer broader therapy options even without significant eosinophilia, with measurable outcomes (NPS, congestion, olfaction) and 16-24-week monitoring [114].

In the phase-3 WAYPOINT trial involving adults with uncontrolled severe CRSwNP, tezepelumab significantly improved NPS, congestion, and SNOT-22 scores, and nearly eliminated the need for surgery or oral corticosteroids use compared to placebo; these effects were rapid, sustained up to 52 weeks, and consistent across subgroups, indicating activity beyond eosinophilia (including "non-eos" phenotypes) [116-118]. Based on the WAYPOINT results, in October 2025, the FDA approved tezepelumab for CRSwNP in patients aged 12 years and older, with a safety profile similar to that observed in patients with severe asthma [119].

Pediatric relevance

Approval for patients aged 12 and older offers an on-label pathway for adolescents with T2-high (and possibly T2-low/"non-eos") CRSwNP who do not respond to standard treatment. Selection based on target pathways (upstream TSLP versus downstream pathways) should consider clinical phenotype, available biomarkers, and goals such as improving olfaction and reducing surgery or oral corticosteroid use. Assessments should be made every 16-24 weeks using NPS, SNOT-22, and smell testing [116,117,119].

Updated regulatory notes (USA/EU)

In the USA, the FDA approved the CRSwNP extension as an add-on

therapy for adults and adolescents aged ≥ 12 years in October 2025, supported by the phase 3 WAYPOINT results (reductions in NPS and congestion, and decreased need for systemic steroids and surgery) [119]. In the EU, approval for CRSwNP (adults) was announced in October 2025 [120].

4.6 New monoclonal antibodies in development (landscape 2024-2025)

In recent years, the pipeline for CRSwNP has expanded to include antibodies that target upstream epithelial alarmins or adopt long-acting strategies, redefining both the timing and goals of therapy beyond the traditional IL-4/IL-13, IL-5, and IgE axes. Among these, depemokimab (GSK3511294) exemplifies the "ultra-long-acting" anti-IL-5 approach: twice-yearly dosing met the co-primary endpoints in ANCHOR-1/2, with clinically and statistically significant reductions in the total NPS and nasal obstruction, along with a favorable safety profile [121] high potency, and an extended half-life, enabling twice per year dosing and sustained type 2 inflammation inhibition. The ANCHOR-1 and ANCHOR-2 trials investigated the efficacy and safety of depemokimab in people with CRSwNP.\ nMETHODS: ANCHOR-1 and ANCHOR-2 were randomised, double-blind, placebo-controlled, parallel-group, replicate phase 3 trials conducted concurrently at 190 centres (hospitals, specialised clinics, and clinical trial sites. The appealing concept is to stabilize the eosinophilic network with a dosing schedule that reflects the chronic, relapsing nature of the disease, effectively "spreading" the pharmacologic effect over 12 months and potentially improving adherence [121].

Beyond IL-5 signaling, focus increasingly shifts to epithelial alarmins. Itepekimab, an anti-IL-33 monoclonal antibody, exemplifies this "upstream" approach. The rationale is to intercept the inflammatory cascade before it branches into traditional T2 pathways, offering potential advantages in non-eosinophilic or mixed phenotypes. The drug is currently in phase 3 trials for CRSwNP (NCT06834347) and is supported by a growing clinical program, with press releases reporting positive results on key endpoints in asthma and a formal development extension for CRS. If these results are confirmed, they could expand the number of candidates suitable for an alarmin-targeted strategy that relies less on conventional T2 biomarkers.

On the IL-13-focused front, lebrikizumab (LY3650150) is testing the hypothesis that selective IL-13 blockade benefits CRSwNP. A phase 3 study (CONTRAST-NP; NCT06338995) is assessing reductions in NPS and congestion on an INCS background; the flexible maintenance schedule (from Q2W to Q4W/Q8W) aims to balance efficacy with treatment sustainability [123]. IL-13 targeting may be especially beneficial for patients with significant epithelial barrier dysfunction and an IL-13-driven transcriptional signature.

Concurrently, a new class of anti-IL-4Rα molecules, similar to dupilumab, is emerging. Stapokibart (CM310) demonstrated positive results in the phase 3 CROWNS-2 randomized clinical trial, published in JAMA in 2025, showing significant improvements in NPS and symptom scores compared with placebo at 24 weeks in patients with severe, uncontrolled CRSwNP [124,125]. These findings, consistent with IL-4/IL-13 biology, suggest that differences in molecular design, pharmacokinetics, and epitope binding could offer alternative options for patients who need choices beyond the current anti-IL-4Rα therapies. Similarly, GR1802, another next-in-class anti-IL-4Rα agent, showed significant improvements in NPS and congestion in uncontrolled CRSwNP in a randomized trial in 2025 , with an overall favorable tolerability profile [126]. Collectively, these signals support the idea of intra-class competition, which could inform more personalized treatment choices based on clinical profile, comorbidities, preferences, and access. Finally, it is important to monitor the IL-33/ST2 axis. While astegolimab (anti-ST2, the IL-33 receptor) does not yet have published data in CRSwNP, a phase 2b trial in severe asthma showed reductions in exacerbations even among eosinophil-low patients, with a reassuring safety profile [127,128]. For CRS, this translates into a credible rationale for future trials in T2-low/mixed phenotypes, where targeting the epithelial source of danger signaling could become game-changing.

5. BIOMARKERS AND PATIENT SELECTION

Selecting pediatric candidates for advanced therapies, including off-label biologics in adolescent CRSwNP, requires a genuinely integrated phenotype-endotype framework in which biomarkers from blood and local compartments are interpreted alongside reproducible clinical and instrumental measures. In practice, a minimal panel already supports better decision-making: peripheral blood eosinophils, total/specific IgE, FeNO (and, where available, nNO/FnNO), combined with endoscopic assessment and standardized outcome scales (e.g., SNOT-22, NPS, olfactory testing) [28,129,130]. This is not just a simple checklist but rather a clinical guide: it directs the choice of therapeutic target (along the IL-4/IL-13, IL-5/IL-5R, IgE, or TSLP pathways), helps set realistic goals (reducing surgery/systemic steroids, restoring olfaction, improving quality of life), and provides objective measures for response evaluation at 16-24 weeks [28,129]. In younger children – where non-T2 patterns and the adenoidal/biofilm ecosystem play a bigger role – biomarker profiling mainly serves to exclude a clinically relevant T2-high endotype; in contrast, in adolescents with CRSwNP and allergic multimorbidity, it enables clinicians to prioritize targeted pathways and, where possible, to participate in registries and prospective studies [131-133] .

5.1 Peripheral and tissue eosinophils

Blood eosinophilia remains the simplest yet most informative marker of the T2 endotype: it correlates with disease severity, recurrence, and – across adult and mixed cohorts – with the likelihood of response to anti-IL-5/anti-IL-5R therapies and, to a lesser extent, to anti-IL-4Rα [86,108,121]. Cutoffs between 150 and 300 cells/μL enhance clinical stratification in adult CRSwNP, while tissue eosinophilia and histologic scores predict postoperative relapse and the need for re-

intervention. Although these findings are mainly derived from adult studies, they are applicable to adolescents – where the overlap of eosinophilia, T2 asthma, and nasal polyposis is common – and they support steroid- and surgery-sparing approaches centered on anti-IL-5/anti-IL-5R biologics or, alternatively, on the IL-4/IL-13 pathway [129,131-133].

5.2 Total, specific, and local IgE

Total/specific IgE indicates systemic atopic burden and, along with clinical history, helps identify an IgE-dependent phenotype that may respond to omalizumab [7,8]. In CRSwNP, however, the biology extends beyond systemic allergy: local intrapolyp IgE – even without serologic sensitization – has been repeatedly observed and is linked to IgE+ B plasma cells, tissue remodeling, and persistence of inflammation [108,134]. In advanced centers, directly measuring local IgE (through lavage or biopsy) can improve patient selection for anti-IgE therapy; when such testing is not available, a strong systemic atopic profile serves as a useful clinical proxy for making a rational choice [108,134].

5.3 Nitric oxide

FeNO, nNO, and FnNO. FeNO is a non-invasive biomarker of eosinophilic T2 airway inflammation, extensively validated in pediatric asthma, and useful for contextualizing CRSwNP when rhinitis or asthma coexist, thereby guiding considerations toward anti-IL-4Rα or anti-TSLP (upstream) and anti-IL-5/IL-5R (downstream) [3,10]. Recent pediatric data show that FeNO and FnNO (nasal fraction) improve stratification and monitoring in children with allergic respiratory disease; in parallel, nNO (nasal air) tends to be reduced in CRSwNP compared to controls and may indicate obstruction, remodeling, and mucociliary dysfunction [30,135-137] . Although specificity for pediatric CRS is limited, combining FeNO/nNO/FnNO with the clinical-endoscopic assessment enhances active T2 inflammation evaluation and supports escalation decisions [138-140].

5.4 T2-signature transcriptomic panels

Where available (e.g., adolescents scheduled for FESS or in specialized centers), polyp tissue biopsies show tissue eosinophilia, mucous gland hyperplasia, and upregulation of T2 genes/mediators (IL-5, IL-13, TARC/CCL17, periostin), thus defining a T2 signature linked to a better response to biologics and reduced surgical interventions [141].

5.5 Biomarker combinations and predictive models

Multimarker approaches combining eosinophils, IgE, FeNO, endoscopy/imaging, and clinical variables (such as age, T2 comorbidities, and severity) better identify high-risk groups with uncontrolled or relapsing disease and identify patients who are more likely to respond to biologics. Cluster methods and decision-tree models that integrate tissue and blood eosinophils, CT scores, age, and comorbidities have improved the prediction of uncontrolled CRSwNP in adult groups, providing transferable principles for pediatric selection – especially during adolescence [142-144]. The goal is not "biomarkers for everyone", but rather biomarkers to enhance decision-making – and to reduce their use when the likelihood of benefit is low. In short, biomarkers do not replace clinical judgment: they sharpen it.

6. PEDIATRIC RESEARCH AGENDA AND SAFETY MONITORING

Despite the significant advances achieved in adults with CRSwNP, the evidence base remains fragmented and mostly extrapolated from other T2 diseases like asthma and atopic dermatitis, as well as from real-world series. Recent clinical reviews and research reiterate the urgent need for dedicated randomized trials, validated pediatric endpoints, and prospective registries that harmonize phenotypes, endotypes, and outcome measures, all while accounting for the anatomical, physiological, and clinical specificities of the developing child. At the same time, current analyses of biologics in CRSwNP stress the importance of biomarker-guided predictive models-using blood and tissue eosinophils, total/local IgE, FeNO, and tissue "T2-signature" panels-along with cost-effectiveness evaluations and pragmatic comparisons with the stepwise surgical approaches typical in pediatric patients (adenoidectomy followed, when necessary, by selective FESS). Within this framework, several research priorities emerge. First, truly pediatric RCTs are needed, enrolling adolescents aged 12-17 years and, when appropriate, children aged 6-11 years, to evaluate effectiveness and safety in populations that differ biologically from adults. Children, especially those under 12, bear a significant burden of non- T 2/adenoid- driven patterns, while adolescents with T 2- high CRSwNP require trials that assess not only symptom and polyp outcomes but also de-escalation strategies (such as gradual withdrawal after remission) and the sustainability of control. Second, pediatric endpoints and standardized core-outcome sets must be established. Beyond NPS and key nasal symptoms, outcome assessments should include SNOT-22 in adolescents, pediatric QoL tools, age- appropriate smell testing, and genuinely patient-centered metrics (such as school attendance, sports participation, and sleep). Consistent timing, followed by durability assessment, and shared criteria for "disease control" are crucial for consistent trial interpretation across centers. Third, biomarkers and selection models should be validated prospectively. Combinations of peripheral and tissue eosinophils (nasal cytology for less invasiveness compared to histology), total and specific (and where feasible, local) IgE, FeNO (± nNO/FnNO), and endoscopic or imaging signs should feed decision-tree models that predict response, minimize unnecessary biologic use, and help guide target selection (upstream versus downstream) in daily pediatric practice. Fourth, registries and real- world pediatric evidence are necessary to capture adherence, reasons for discontinuation, switching/swapping biologics, adverse events, and resource use. Incorporating longitudinal biomarkers (eosinophils, FeNO) will support comparative-effectiveness and cost-effectiveness analyses in real-world conditions.

Safety monitoring must advance alongside this research agenda. Current pediatric safety summaries, mainly based on asthma and atopic dermatitis, show a positive safety profile for dupilumab, mepolizumab, benralizumab, and omalizumab, with no new safety concerns appearing in long-term follow-up. Across all pediatric ages, growth and pubertal development should be documented longitudinally. Although T2 biologics are not systemic corticosteroids, recording auxology remains good pediatric practice and reassures families that development is being monitored.

Communication and consent are crucial for safe, long-lasting care. Informed consent should clearly cover on-/off-label use, expected benefits, alternatives (such as optimized SOC and stepwise surgery), remaining uncertainties (especially the lack of pediatric RCTs for many conditions), and the monitoring plan. Active involvement of families and, when suitable, the adolescent (assent) enhances adherence and ongoing treatment. Lastly, health-economic factors must not be overlooked. Adult CRSwNP cost-effectiveness studies show varied results depending on initial severity, response trajectories, and how much OCS and surgery are avoided; translating this to children will need real-world evidence that includes child-specific outcomes (like school attendance and caregiver burden) alongside traditional clinical results to guide reimbursement and sustainability.

In summary, a pediatric roadmap should incorporate dedicated RCTs with child-friendly endpoints, multicenter registries with longitudinal biomarkers, and harmonized pharmacovigilance plans. This approach provides a clear opportunity to develop a targeted and sustainable use of biologics in adolescent CRSwNP, based on biomarkers and structured monitoring.

7. CONCLUSION

The comprehensive research on monoclonal antibodies and biologic therapies in pediatric chronic rhinosinusitis, especially in cases with nasal polyposis, indicates a significant shift in treatment strategies. Biologic agents targeting type-2 inflammatory pathways have shown considerable promise in better symptom management, shrinking nasal polyps, and improving quality of life. Among these, dupilumab consistently stands out as the biologic with the strongest efficacy profile. This progress in treatment is especially valuable given the limitations of standard medical and surgical options in cases that do not respond to traditional approaches.

The safety profiles of these biologics are generally favorable, with adverse events mainly being mild to moderate. Transient eosinophilia linked to specific agents usually does not require stopping treatment, although long-term safety data specifically for pediatric populations are still limited and need further investigation. The lack of randomized controlled trials focused on children – and the common reliance on adult or mixed-age cohort data – creates a significant research gap, underscoring the need for thorough, pediatric-specific studies to inform dosing, safety monitoring, and treatment duration.

Biomarker research emphasizes the diverse nature of pediatric chronic rhinosinusitis and the challenge of predicting responses to biologic therapy. Peripheral blood eosinophil counts show some promise as predictors of dupilumab effectiveness, but the overall reliability and clinical value of biomarkers like serum IgE and local IgE are still limited. This variability highlights the need for personalized, endotype-based treatment strategies, even though universally accepted biomarkers and standardized response criteria are not yet fully established. Long-term data suggest that biologics can reduce recurrence rates and the need for surgery, but limited extended follow-up data are available. Increasingly, integrating biologic therapies into multidisciplinary pediatric care teams is recommended, as it combines the expertise of allergists, immunologists, and otolaryngologists to address the complex factors of the disease.

Persistent challenges include access, affordability, and the development of standardized clinical guidelines that customize biologic use based on individual patient profiles. In summary, biologic therapies mark a significant advancement in managing pediatric chronic rhinosinusitis with nasal polyps, providing targeted, effective, and generally safe treatment options that complement – or potentially replace – conventional therapies. To realize their full potential, it is crucial to expand pediatric clinical trials, validate biomarkers for patient selection and monitoring, and establish cohesive multidisciplinary frameworks that integrate biologics into comprehensive care pathways.

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Author's contributions

A.G. conceived, designed, and wrote the manuscript. All authors contributed to critical revision of the work and approved the final version.

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