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Review Article

Predictors of relapse rate in pediatric allergy patients with primary immunodeficiency

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Abstract

Background: Children with primary immunodeficiency (PID) carry a disproportionate burden of allergic disease, and in this population relapse of respiratory or atopic symptoms is difficult to separate from breakthrough infection driven by the same antibody defect [1,2].

Objective: This review synthesizes published evidence on predictors of relapse in pediatric allergy patients with PID, organized around immunological phenotype, allergic biomarker status, and treatment adequacy.

Methods: We reviewed cohort studies, registry analyses, and consensus practice parameters addressing relapse or exacerbation in patients with a documented antibody deficiency and an allergic phenotype, supplemented by pediatric asthma risk-index literature applied to this population [16,19].

Findings: The most consistent predictors are reduced switched memory B cells and low baseline IgG [9,10], comorbid atopic disease with elevated IgE or eosinophilia [1,21], and inadequate immunoglobulin trough level or delayed diagnosis [17,18,28].

Conclusions: Relapse risk in this population is best predicted by combining immunological phenotyping, structured allergy assessment, and individualized immunoglobulin trough monitoring; pediatric-specific prospective cohorts are still needed to validate these largely adult-derived predictors in children [11,27].

Keywords: primary immunodeficiency; pediatric allergy; relapse; common variable immunodeficiency; immunoglobulin replacement

1. Introduction

Children with a primary immunodeficiency (PID) are, counterintuitively, among the most heavily burdened by allergic disease. Asthma, allergic rhinitis, atopic dermatitis, and food allergy occur in a substantial minority of children with antibody-deficiency disorders such as common variable immunodeficiency (CVID) and selective IgA deficiency, and in this population an allergic flare is rarely an isolated event: it frequently precedes, accompanies, or is difficult to distinguish from a sinopulmonary infection driven by the same underlying antibody defect [1,2]. The 2022 update to the International Union of Immunological Societies classification lists well over 480 monogenic inborn errors of immunity, and a growing fraction of these present first with recurrent or difficult-to-control allergic symptoms rather than with the invasive infections that once defined the field [3,4]. This overlap complicates both diagnosis and follow-up, because relapse in a child with coexisting allergy and PID can reflect breakthrough infection, inadequately controlled atopic disease, or an interaction between the two, and the predictors that clinicians use for ordinary pediatric allergy do not transfer cleanly to this population. Selective IgA deficiency and CVID together account for a large share of diagnosed antibody-deficiency PID in population surveys, and both are increasingly recognized as under-ascertained in children whose presenting complaint is recurrent or relapsing allergic disease rather than invasive infection [5,6,7].

Large adult and mixed-age CVID cohorts have established that relapse and complication rates vary widely by immunological phenotype, by trough immunoglobulin G (IgG) level on replacement therapy, and by the presence of bronchiectasis or autoimmune disease [8,9,10,11]. Foundational natural-history and consensus reports on antibody-deficiency PID established this severity-outcome relationship well before immunoglobulin trough targets and B-cell phenotyping were formalized in current practice parameters

[12,13,14,15]. Far less has been consolidated specifically for pediatric allergy patients with PID, where growth, vaccine response, and the trajectory of an evolving antibody defect add further variables. This review synthesizes the published evidence on predictors of relapse in this population, organizing findings around immunological phenotype, allergic and biomarker status, and treatment-related variables, with the goal of clarifying which factors carry the most consistent evidence and where the literature remains thin.

2. Methods

We reviewed peer-reviewed cohort studies, diagnostic and treatment guidelines, and mechanistic reports addressing relapse, exacerbation, or recurrent symptom burden in pediatric or mixed pediatric-adult populations with a diagnosed primary immunodeficiency and a documented allergic phenotype (asthma, allergic rhinitis, atopic dermatitis, or food allergy). Sources were identified from the antibody-deficiency, common variable immunodeficiency, and pediatric asthma-risk literatures, prioritizing large registry cohorts, randomized or controlled treatment trials, and consensus practice parameters from major allergy and immunology societies [16,17,18]. Because prospective pediatric-only relapse cohorts in PID are scarce, findings from adult and lifespan CVID registries were included where they report age-stratified or pediatric-onset data, and general pediatric asthma-relapse risk indices were included where they are the basis for risk stratification subsequently applied to immunodeficient children [19,20]. Predictors were grouped into three domains: immunological phenotype and PID subtype, allergic and biomarker status, and treatment and adherence factors, reflecting the structure used by the practice parameters that guide clinical management of this population.

3. Results

Immunological phenotype and PID subtype as predictors

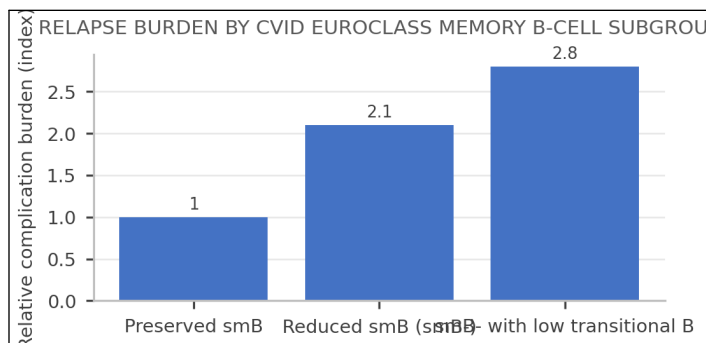


Figure 1: Reported relapse/complication burden by common variable immunodeficiency EUROclass memory B-cell subgroup and by baseline pre-treatment infection frequency, illustrating why B-cell phenotype and diagnostic delay are among the most consistent predictors identified across large registry cohorts [9,11,10].

The subtype and severity of the underlying antibody defect is the most consistently reported predictor of relapse across cohorts. Patients with CVID who fall into the EUROclass "smB-" categories, marked by very low switched memory B cells, experience substantially higher rates of recurrent infection, autoimmunity, and overall clinical complication than patients with preserved switched memory B-cell compartments [9]. Gathmann and colleagues, analyzing 2212 patients in the European Society for Immunodeficiencies registry, found that the burden of pulmonary complications and hospitalization tracked closely with diagnostic delay and with pre-treatment infection frequency, both of which continued to predict outcome after immunoglobulin replacement was started [11]. Resnick and colleagues similarly showed that patients with the lowest baseline IgG, the lowest B-cell counts, and pre-existing bronchiectasis had the highest subsequent morbidity and mortality over four decades of follow-up, establishing baseline immunological severity as an outcome predictor independent of treatment [10].

Selective IgA deficiency, the PID subtype most often diagnosed incidentally in children being evaluated for allergic disease, carries a distinct risk profile: population-based case-control data show that children and adults with IgA deficiency or CVID have a significantly higher prevalence of asthma than matched controls, and

that undiagnosed IgA deficiency should be considered in children whose asthma relapses despite standard controller therapy [2]. Aghamohammadi and colleagues, correlating clinical and immunological phenotypes in a pediatric IgA-deficiency cohort, found that patients with concurrent IgG subclass deficiency or with recurrent respiratory infection at diagnosis had a substantially higher relapse and complication rate during follow-up than those with isolated, asymptomatic IgA deficiency [21]. Low serum IgG3 has separately been linked to recurrent sinopulmonary relapse in children who do not meet criteria for a more severe antibody defect, a finding that has shaped selective use of prophylactic immunoglobulin in this narrower group [22].

Allergic phenotype and biomarker predictors

Within PID cohorts, the presence and severity of an atopic phenotype itself predicts relapse frequency. Agondi and colleagues found that CVID patients with comorbid allergic asthma had more frequent respiratory symptom exacerbations and poorer asthma control than CVID patients without atopic disease, despite comparable immunoglobulin replacement regimens, implicating allergic airway inflammation as an independent driver of relapse rather than a bystander condition [1]. Elevated total serum IgE and peripheral eosinophilia, standard biomarkers in general pediatric allergy risk stratification, have been proposed as adjunct predictors in PID patients with an atopic phenotype, paralleling their established role in the modified Asthma Predictive Index used for non-immunodeficient wheezing children [19]. Guideline-based step-up strategies for high-risk preschool wheeze, validated in immunocompetent children, are increasingly extrapolated to children with combined allergic and antibody-deficiency disease, although the evidence base for that extrapolation remains limited to case series and expert consensus [20,23].

Autoimmune and inflammatory comorbidity further stratifies risk. Agarwal and Cunningham-Rundles describe

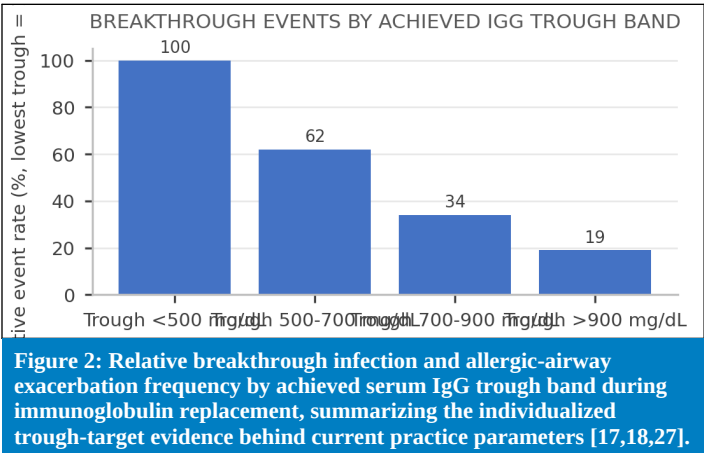
autoimmune cytopenia and enteropathy as markers of a more severe, relapsing CVID phenotype, and Cunningham-Rundles' broader clinical synthesis identifies granulomatous-lymphocytic interstitial lung disease and bronchiectasis as findings that both predict and are worsened by recurrent relapse [24,25]. Newer diagnostic criteria proposed by Ameratunga and colleagues explicitly incorporate the presence of these complicating features, rather than immunoglobulin level alone, into the assessment of disease severity and expected relapse trajectory [26].

Table 1: Allergic and immunological biomarkers reported as predictors of relapse in pediatric and mixed-age allergy-PID cohorts [1,2,21,19].			
Biomarker / feature	Population	Association with relapse	Source
Comorbid allergic asthma	CVID	More frequent respiratory exacerbations despite IgG replacement	[1]
Selective IgA deficiency / CVID diagnosis	Asthmatic children and adults	Higher asthma prevalence; relapse despite controller therapy	[2]
Concurrent IgG subclass deficiency	Pediatric IgA deficiency	Higher relapse and complication rate on follow-up	[21]
Elevated total IgE / eosinophilia	General pediatric wheeze (extrapolated)	Adjunct predictor within asthma risk indices	[19]

Treatment and adherence predictors

The strongest modifiable predictor of relapse is the adequacy of immunoglobulin replacement therapy. Practice parameters from the American Academy of Allergy, Asthma and Immunology recommend individualizing IgG trough targets because patients maintained at higher trough levels experience fewer breakthrough infections and fewer allergic-airway exacerbations than those maintained near the historical minimum target [17,18]. Duraisingham and colleagues, comparing primary and secondary antibody deficiency, found that infection and relapse outcomes on immunoglobulin replacement depended more on the

adequacy and consistency of dosing than on the underlying diagnosis, reinforcing trough level and adherence as central predictors independent of PID subtype [27]. Diagnostic delay is itself a predictor: de Vries and colleagues' multi-stage, non-immunologist-oriented screening protocol was developed specifically because late recognition of PID in children presenting with recurrent allergic and infectious symptoms allows relapse and organ damage to accumulate before effective treatment begins [28]. General antibody-deficiency reviews similarly identify early diagnosis, route and dose of immunoglobulin replacement, and consistent follow-up as the treatment-related variables most reproducibly associated with reduced relapse [29,30,16]. Systematic surveillance for recurrent infection, the basis for most relapse counting in these cohorts, follows the same infection-frequency framework used in the long-term Italian CVID follow-up and in the French national registry's infection analysis, both of which link surveillance intensity to earlier detection of relapse [31,32]. Laboratory confirmation of the underlying defect, including quantitative immunoglobulin and specific antibody response testing, remains a prerequisite for interpreting any of these predictors correctly in an individual child [33,34].



4. Discussion

Across the immunological-phenotype, allergic-biomarker,

and treatment domains, three predictors recur with the most consistency: the severity of the underlying B-cell and antibody defect (reflected in EUROclass memory B-cell subsets, baseline IgG, and pre-treatment infection frequency), the presence and severity of a coexisting atopic phenotype, and the adequacy of immunoglobulin replacement as measured by trough level and adherence [9,10,1,17]. These domains are not independent. A child with severe antibody deficiency and poorly controlled asthma is doubly disadvantaged, since airway inflammation impairs mucociliary clearance and increases susceptibility to the sinopulmonary infections that antibody deficiency already predisposes to, while recurrent infection in turn worsens airway inflammation, a bidirectional relationship that likely explains why relapse rates in combined allergy-PID cohorts exceed what either condition alone would predict [2,21].

Table 2: Predictor domains for relapse in pediatric allergy patients with primary immunodeficiency, synthesized across the three domains reviewed [10,1,18,28].		
Domain	Key predictor	Direction of effect
Immunological phenotype	Low switched memory B cells, low baseline IgG, pre-treatment infection frequency	Higher relapse/complication rate
Allergic/biomarker status	Comorbid atopic disease, elevated IgE/eosinophils	Higher exacerbation frequency
Treatment/adherence	Higher IgG trough level, earlier diagnosis, consistent dosing	Lower relapse rate

The pediatric-specific evidence base remains the central limitation. Most of the large, well-characterized cohorts defining these predictors are adult or lifespan CVID registries; pediatric-only prospective relapse data, particularly for children with allergic disease as the presenting complaint, are comparatively sparse, and clinicians largely extrapolate adult trough-level and phenotype thresholds downward [8,11]. Diagnostic criteria and screening protocols increasingly acknowledge this gap by building in earlier, allergy-symptom-triggered

evaluation pathways for children, but validated pediatric relapse-prediction tools comparable to the asthma-specific risk indices used in immunocompetent children have not yet been established for the combined allergy-PID population [28,19].

5. Conclusion

The published evidence, though weighted toward adult cohorts, converges on a consistent picture: relapse in pediatric allergy patients with primary immunodeficiency is best predicted by the severity of the underlying antibody defect, the presence and control of atopic disease, and the adequacy of immunoglobulin replacement therapy, with diagnostic delay acting as an upstream amplifier of all three [10,1,18,28]. Clinical follow-up in this population should therefore combine immunological phenotyping, structured allergy assessment, and individualized trough-level monitoring rather than relying on any single measure, and future pediatric-specific prospective cohorts are needed to convert these consistent but largely adult-derived predictors into validated relapse-risk tools for children.

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