CLINICAL AND LABORATORY EVIDENCE LINKING ALLERGY AND ACUTE OR CHRONIC RHINOSINUSITIS IN CHILDREN.

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Abstract

Background: allergic rhinitis is a common childhood disease in industrialized countries that is responsible for a major impact on quality of life and health care resources. The objective of this review was to provide a systemic review of experimental and clinical evidence linking allergy to rhinosinusitis in children including common cold. Furthermore, we questioned if anti-allergy treatment may prevent the occurrence of rhinosinusitis or improve outcomes of its specific management. Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) process to identify experimental and clinical articles about allergy and acute or chronic rhinosinusitis in children published since January 2000. The research was performed in April 2020 including only English-language peer-reviewed papers. Our search yielded 7103 that were finally screened. This resulted in 30 publications of which the full texts were assessed and included in a qualitative analysis per different phenotypes of rhinosinusitis. Results: The evidence suggests that allergy may lead to overall impairment of mechanical and immunological defense function of the nasal mucosa against viruses and that anti-allergy treatment may significantly decrease the number and severity of upper respiratory tract infections including common colds in children. It was not possible to perform the analysis for allergy and post viral acute rhinosinusitis, bacterial acute rhinosinusitis and recurrent acute rhinosinusitis because of paucity and heterogeneity of data. We found interesting data linking allergy to chronic rhinosinusitis: although there is no definitive proof of causation studies lead to suppose that anti-allergy treatment may improve outcomes of specific CRS treatments. Conclusion: We summarized conclusions in a practical algorithm taking into account different phenotypes of rhinosinusitis in order to elucidate when prompt and accurate diagnosis of allergy is recommended. We lastly focused attention on the needs for future research.

INTRODUCTION.

Allergic rhinitis (AR) in children has a significant impact on global quality of life, including school performance, sleep disorders, and emotional health[2]. Furthermore, over the years many authors tried to correlate allergy with comorbidities and in particular to the onset of rhinosinusitis including common cold, even though conflicting results are frequently reached.

AR is a nasal mucosa inflammatory condition caused by environmental allergens interacting with immunoglobulin (Ig) E in sensitized subjects. Repeated exposure may lead to long-term changes in systemic

and local inflammation, including up-regulation of nasal eosinophils and allergen-specific IgE, increased levels of adhesion molecules in airway mucosa and enhanced systemic response to allergen challenge[4]. Consequently, it is not surprising that AR has been historically associated with comorbid upper airway diseases[5]. Herein, we review clinical and laboratory evidence, linking allergy to rhinosinusitis in children. We aimed to investigate allergy not only as etiologic, but also as a worsening factor; in fact, poorly controlled AR might contribute to exacerbations and as such its adequate treatment might improve outcomes[6].

Material and methods.

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) process to identify published experimental and clinical articles about allergy and rhinosinusitis including common cold in children. Manuscript were screened primarily by Ovid Medline and EMBASE and from other sources (Pubmed Central, Cochrane review, Web of Science, and Google Scholar) and published from January 2000 to April 2020. Only 3 articles before this date were included because considered particularly relevant for this systematic review. Literature searches were performed in April 2020.

We performed two different searches using MeSH-terms. One group of authors focused on *experimental studies* matching the term as follow: ((Rhinovirus) OR (coronavirus) OR (epithelial barrier) OR (epithelial cells) OR (barrier function) OR (nasal epithelial cells) OR (viral infections)) AND ((Allergy) OR (Allergic rhinitis) OR (Atopy) OR (Atopic) OR (Allergic Children) OR (Non allergic children) OR (immunoglobulin E)) AND ((children) OR (childhood) OR (pediatric)). The second group of authors focused on *clinical studies,* matching the term as follow: ((respiratory infections) OR (acute rhinosinusitis) OR (Chronic rhinosinusitis) OR (Sinusitis) OR (Rhinosinusitis) OR (Recurrent sinusitis) OR (endoscopic sinus surgery) OR (URTI) OR (Upper Recurrent Respiratory Infection)) AND ((Allergy) OR (Allergic rhinitis) OR (Atopy) OR (Atopic) OR (Allergic Children) OR (Non allergic children) OR (immunoglobulin E) OR (immunotherapy) OR (antihistamine)) AND ((children) OR (childhood) OR (pediatric)).

Study selection.

In the first screening authors read the title and abstract of articles selecting those being as inclusive as possible. The abstracts were screened independently by reviewers of the two groups. Any disagreements were resolved by consensus. Inclusion and exclusion criteria were established before the selection of relevant studies. The inclusion criteria were primary research (including descriptive studies, observational studies, randomized trials, and basic science articles), published after January 2000, addressing allergy and rhinosinusitis in children including common cold. Furthermore, we questioned if anti-allergy treatment may prevent the occurrence of rhinosinusitis or improve its specific management.

We excluded secondary research studies (e.g., review articles or systematic review), case studies, newspaper article, lecture, letter, comment, personal narrative, consensus conference, editorial. Only articles with full text available were included. Additional studies were manually identified from the reference lists of retrieved literature. We excluded all the article that did not meet the inclusion criteria or deal directly with the issue investigated. We made exceptions for experimental models including studies on cultured epithelial cells obtained from adults, which are obviously more frequent than from children. Based on our review was not possible differentiate between atopy or sanitization and allergy. We included only English-language peer-reviewed papers.

RESULTS

The details of the systematic search performed are shown in Fig. 1. In total, our search yielded 9870 after duplicates removal. We excluded 2767 due to time of publication and type of article, then 7103 were finally screened. This resulted in 30 publications of which the full texts were assessed and included in a qualitative analysis. We summarized in tables the included studies per each phenotype classifying evidence using GRADE methodology. No studies were included in a quantitative synthesis (meta-analysis).

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Allergy and acute rhinosinusitis in children.

According to the EPOS2020 guidelines[7], acute rhinosinusitis in children (ARS) is defined as a sudden onset of two or more of the following symptoms: nasal blockage/obstruction/congestion, discoloured nasal discharge and cough (daytime and night-time) for<12 weeks. ARS in children can theoretically be divided into viral acute rhinosinusitis (i.e. common cold), post-viral rhinosinusitis, acute bacterial rhinosinusitis (ABRS). Acute viral rhinosinusitis has usually a duration of symptoms of <10 days. Post-viral one is defined if symptoms increase after five days, or are persistent for more than 10 days, with less than 12 weeks duration; only a small subgroup of these are of bacterial origin. Discolored mucous, severe pain, fever >38, "double sickening" lead to the suspicious of bacterial supra infection. Recurrent ARS(RARS) is defined as [?]4 episodes of rhinosinusitis per year with symptom-free intervals.

Allergy and acute viral rhinosinusitis in children (i.e common cold) including viral upper respiratory tract infections (URTIs).

Viral acute rhinosinusitis (i.e common cold) may be induced in children by a wide variety of viruses, such rhinoviruses (RV) and coronaviruses (CorV), as well as respiratory syncytial virus (RSV), parainfluenza viruses and adenoviruses. The common cold is the most frequent upper respiratory tract infection (URTI), which are the most commonly treated acute problems in primary pediatric care[8]. URTI are caused mainly by viruses and may involve not only nose and sinuses but also pharynx, larynx, and large airways. Clinical expression of URTIs is variable and it is influenced by the nature of the infecting virus, by the age and by physiological state and immunological experience of the host. Sino nasal clinical features of common cold or URTI commonly overlap and are characterized by self-limiting irritation of the upper airways with associated cough with no proof of pneumonia[9]. Based on our review of the literature we observed that authors for research purpose include common colds in URTI; for this reason, we included both papers about allergy and common cold or URTI.

1.1.1 Laboratory evidence linking allergy to increased risk of epithelial cells viral infection.

All experimental studies included in the qualitative analyses suggest that allergy may increase the risk of viral infections of upper airways epithelial cells consequent to Th2-polarization (Table I). The mechanisms involved may be related to enhanced adherence of pathogens to inflamed respiratory epithelium, increased mucosal permeability, altered immune response to certain viral pathogens, and excessive mucus production and modifications of mucus consistency as pabulum for microbe overgrowth[10].

Allergy may induce inflammation of the nasal mucosa leading to*impairment of epithelial barrier function* and secondary deficiency of early local immune reaction. Several studies demonstrated, in fact, that the upper airway epithelium represents not only a mechanical wall against pathogens by muco-ciliary clearance, but also an immunological barrier modulating the innate immune response through cytokine production[11].

Interestingly, authors[12,13] demonstrated impairment of the overall *mechanical function of the epithelium* and, in particular, decreased expression of tight-junction proteins occludin and zonula occludens-1 in cultured epithelial nasal cells from allergic patients. Steelant et al.[14] demonstrated that nasal secretions from allergic subjects rapidly decrease the trans-tissue resistance of epithelial cell cultures in vitro. They also showed that anti-IL-4 treatment in mice prevented epithelial barrier disruption. Finally, several authors have demonstrated[15,16] that allergy may expedite viral overcome of mechanical barriers because TH-2 polarized cytokines such as IL-4, IL-5, and IL-13 can upregulate endothelial and epithelial expression of adhesion molecules like intercellular adhesion molecule-1 (ICAM-1), which is the receptor for 90% of rhinoviruses.

On the other hand, several authors demonstrated that allergy may modify the *immunological functions of the epithelia.* Many studies showed the deficiency of the innate immune response in allergic mucosa of upper and lower respiratory epithelia cells. Furthermore, it has been demonstrated in the lab that interferon production may be defective in allergic patients. Interferons are crucial for induction of apoptosis in virus-infected host cells because they prevent establishment of viral replication and promote phagocytosis of infected cells[17,18,19]. Accordingly, in 2015 Teach et al.[20] found that peripheral blood mononuclear cells

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cultured from a subset of atopic children treated with anti-IgE improved INF-α production after incubation with rhinovirus.

1.1.2 Clinical evidence linking allergy to risk of viral upper respiratory infection.

From a clinical point of view, the results are more controversial than those from the laboratory. Studies in the literature comparing the incidence of upper respiratory infections between allergic and non-allergic subjects are relatively few in number (see 4 articles included in the qualitative analyses in table II).

In two manuscript has been demonstrated that atopic/allergic patients had increased susceptibility to upper respiratory infections. In 2006, in a large cross-sectional survey Karevold et al.[21]demonstrated that atopy increases the risk of developing upper and lower respiratory tract infections in children. In particular, atopy was the strongest risk factor, such as in the home environment (dampness). Accordingly, Ciprandi et al.[22] observed that allergic children have a significantly higher number of upper respiratory infections, more serious in duration and severity, compared with non-allergic ones.

Other authors disagree: Kværner et al.[23] reported that correlation between upper respiratory infection and atopic diseases from a population-based sample of 7992 Norwegian twins was weak, even though results were inconclusive. Sütçü et al.[24]confirmed that the number of episodes per year was not significantly different between atopic and healthy children, even though atopic ones had longer episodes of recurrent URTI compared to controls.

Interestingly all clinical studies included in the qualitative analyses about therapy (Table II) supported the hypothesis that anti-allergy specific or non-specific treatments may prevent viral infections of the upper airways. Antihistamine therapy can act by reducing the expression of adhesion viral receptors to modulate the production of TH-2 related interleukins[22]. Authors[16,25]demonstrated that children treated with cetirizine had a significant reduction in ICAM-I expression on epithelial cells, thus preventing possible relapse of rhinovirus infections and diminishing both the number and severity of recurrent respiratory infections in children. Barberi et al.[26, 27] demonstrated that children treated with sublingual immunotherapy (SLIT) had significantly fewer respiratory infections (RI) than symptomatically treated children. In addition, SLIT-treated children had less fever episodes per year and took fewer medications vs. symptomatically treated children.

1.2 Allergy and post-viral acute rhinosinusitis and acute bacterial rhinosinusitis (ABRS) in children.

In the articles reviewed we did not find manuscript in which authors distinguished between post viral ARS and ABRS. Authors focused the attention in the particular on the risks of bacterial superinfection. Recent evidence suggests in fact that damage or disruption of mucociliary function due to viral infection is probably a major cause of super- or secondary bacterial infection. Allergy is a condition that potentially can exacerbate an inflammatory sino-nasal response, although very limited data are available to confirm this hypothesis.[28] Based on paucity and heterogeneity of the studies it was not possible to perform a qualitative analysis linking allergy to ABRS or to post viral ARS[7] for this reason we report by a narrative description available data.

Lin et al.[29] demonstrated that the prevalence of colonization by methicillin-resistant S. aureus was higher in atopic children than healthy ones and that atopic children were more likely to develop ARS than nonatopic ones. Interestingly, other authors[30] observed that AR was highly prevalent in orbital ARS complications in children and, specifically, it was found in 64.3% of children with pre-septal cellulitis, in 25% with periostitis, and in 76.5% with subperiosteal abscess. Furthermore, the prevalence of AR was significantly higher in patients presenting in pollen season from February to August than in patients presenting between September and January. The authors suggested that allergy may be a cofactor in the pathogenesis of orbital complication of ARS. In addition, Alho et al.[31] observed that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes in CT scans than non-allergic subjects during viral colds. The authors suggested that these changes were signs of more severely impaired sinus function, increasing the risk of bacterial sinusitis.

Shi-Wei Lin et al.[32] recently evaluated the risk of incident acute rhinosinusitis among children with allergic rhinitis, using a nationwide, population-based health claims research database and including a large number of patients. The authors observed that the risk of acute rhinosinusitis was significantly higher in pediatric patients with allergic rhinitis compared to those without the condition (adjusted hazard ratio = 3.03, 95% confidence interval = 2.89–3.18). Caution is advised when interpreting the findings of the authors due to limitations of the study: retrospective design, diagnosis of ARS based on clinical history (authors could not confirm bacterial etiology of sinusitis).

On the other hand, Leo et al.[33] demonstrated that children with grass pollen induced rhinitis during exposure to pollen had an incidence of endoscopically confirmed ARS comparable to non-allergic children; they consequently suggested that AR was a negligible risk factor for ARS and that the most common risk factor was instead a previous acute viral infection. Accordingly, EPOS 2020 concluded that there appears to be small evidence to support the presence of AR as a risk factor for developing ARS in children, recognizing a central role for previous viral infection.

1.3 Allergy and recurrent acute rhinosinusitis (RARS) in children.

We found very limited and heterogeneous data linking allergy to RARS and it was not possible to perform a qualitative analysis. Choi et al.[34] evaluated the predisposing factors that may be associated with chronic and recurrent RS examining 296 patients with RS younger than 13 years of age. The prevalence of allergic rhinitis, atopy, and asthma were significantly higher in patients with chronic and recurrent RS than those with acute and subacute RS. Veskitkul et al.[35] evaluated the clinical characteristics and predisposing factors of RARS in children as well as the preventive therapy. The authors suggested that allergic rhinitis may be considered a predisposing factor because it was detected in 35.1% of cases, concluding that children with RARS should be always evaluated for the presence of underlying predisposing conditions including allergic disease. Nevertheless, no comparison with a control group was performed and for this reason data are not definitely supporting a link between allergy and RARS.

Allergy and Chronic Rhinosinusitis (CRS) in Children.

Chronic rhinosinusitis (with or without nasal polyps) in children is defined as: presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) with or without facial pain/pressure and/or cough for [?]12 weeks associated to pathognomonic endoscopic signs or CT changes[7]. The prevalence of CRS in children is lower than in adults (2-4%), nevertheless, the negative impact on quality of life seems to be similar to that observed in adults. Studies on CRS in children are less common and it is more difficult to investigate the relationship with allergy[7]. Several factors contribute to complicate the analyses including incomplete evaluation (nasal endoscopy and/or imaging are rarely performed in many children) and the difficulty to differentiate CRS from adenoid hypertrophy, adenoiditis, and (allergic) rhinitis. In fact, nasal blockage may occur in AR children, due to edematous mucosa, neurogenic and vascular responses, over-production of secretions, and impaired muco-ciliary clearance leading to congestion of the ostia and symptoms simulating rhinosinusitis. On the other hand, the blockage leads to stagnant debris and acidotic environment that might stimulate bacteria overgrowth[36, 37].

Histopathological analysis[38,39] demonstrated that pediatric CRS is quite different from the adult form, showing greater inflammatory cellularity, higher density of submucosal lymphocytes, less eosinophilic inflammation, basement membrane thickening, and mucous gland hyperplasia, suggesting a different pathway compared to the adult CRS pattern, which is predominantly characterized by a Th2-oriented response with polypoid changes. The presence of nasal polyps in a pediatric patient should suggest the hypothesis of cystic fibrosis that has not been included in this paper. More specifically, some evidence supports the hypothesis that CRS in children over the age of 13 seems to be based more on eosinophilic inflammation, while under this age CRS seems to be based more on neutrophilic inflammation, thus justifying the lower prevalence of nasal polyps in children than in adult[38, 39].

Several manuscripts support the hypothesis that AR and CRS could be different faces of the same disease.

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AR, in fact, is typically characterized by a Th2 immune response involving IL-4, IL-5 and IL-13 which drives IgE production and recruitment of eosinophil granulocytes. It has been suggested[40-44] that eosinophils, by generating potent toxic agents (cationic proteins, oxygen-free radicals, and proinflammatory cytokines), may play a major role in initiating and perpetuating inflammation of sino-nasal mucosa in patients with AR.

2.1.1 Evidence from the lab linking allergic inflammation to increased risk of chronic rhinosinusitis in children.

All studies included in a qualitative analysis support a specific link between CRS and AR in children (Table III). Chawes[45] studied nasal eosinophilia and nasal airway patency (assessed by acoustic rhinometry) in children with AR, non-allergic rhinitis and healthy controls. Nasal eosinophilia and irreversible nasal airway obstruction were significantly associated with AR, whilst there was no such association with non-allergic rhinitis. The authors suggested that chronic inflammation and structural remodeling of the sino-nasal mucosa may occur in allergic children even at 6 years of age.

Some authors suggested that allergic sino-nasal inflammation may support bacterial infection. Blair et al.[46] in an animal model showed that allergic inflammatory reaction may obstruct sinus drainage encouraging bacterial infection into the maxillary sinus. Shin et al.[47] demonstrated that total IgE, total eosinophil count, and serum eosinophil cationic protein levels were significantly higher in CRS children whose symptoms and radiologic abnormalities did not resolve after 12 weeks despite appropriate antibiotic therapy (non-responder) compared with responders and healthy controls. Moreover, AR in children may affect the efficiency of mucociliary clearance, which is one of the most important protective functions of the respiratory epithelium. Deterioration of muco-ciliary system appears to be related to more severe rhinitis with a higher intensity of local nasal inflammation, reflected in nasal smear eosinophilia[48].

Brożek-Madry and co-workers[49] evaluated the relation between bacterial strains and cytological examination of nasal mucosa in children with CRS; they found that the most common strains of bacteria observed in CRS (Hemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus) were associated with a higher prevalence of atopy and percentage of eosinophils in cytology. It must be noted that S. aureus enterotoxins are able to induce increased severity of the disease, amplifying eosinophilic inflammation in atopic patients[50].

Clinical evidence linking allergic inflammation to increased risk of chronic rhinosinusitis.

The association between allergy and CRS in adults has been discussed for years and a strong association has been observed with particular subtypes of CRS with nasal polyps (wNP), such as central compartment atopic disease and allergic fungal rhinosinusitis[51,52]. Manuscripts on pediatric CRS are less common predominantly because of ethical issues regarding administration of X-rays in the pediatric population. The publications included in the qualitative analyses are summarized in Table IV. Conclusions of the studies included in the qualitative analyses were not unanimously linking allergy to chronic rhinosinusitis.

Several manuscripts seem to support a positive clinical association between AR and CRS, describing a prevalence varying between 27% and 59% of patients[53,54,55]. Brietzke et al.[56] in an expert panel consensus, suggested that there is a clinically-relevant association between AR and pediatric CRS, particularly in older children. Sedaghat et al.[57], analyzing a large series of 4044 pediatric cases, observed that AR is one of the most prevalent comorbidity observed in children with CRS (26.9%) even though a comparison with control group was not provided. Choi et al.[34] showed that age, atopy, AR, and asthma may be predisposing factors for pediatric CRS and recurrent RS. The authors proposed that specific evaluation for allergic diseases should be considered when managing chronic or recurrent RS. More recently, Anamika et al.[58] demonstrated a positive skin prick-test in 53% of the cases in a cohort of 110 children with CRS; moreover, those with atopy had higher mean Lund-Mackay endoscopic score and Sinus and Nasal Quality of Life Survey score than non-atopic patients.

Huang et al.[59] attempted discrimination among different allergies and reported that mold allergy represents a significant risk factor for development of sinusitis, compared to non-mold allergy, in a case series of 413

children followed for 5 years. These data suggest that perennial allergy may be a stronger risk factor for CRS compared to seasonal allergy.

On the other hand, some studies suggested a lack of correlation between allergic disease and pediatric CRS. Leo et al.[60], in a report on 351 children affected by CRS, demonstrated that the prevalence of sensitization to aeroallergens was comparable to that of the general pediatric population. No clinical evidence could account for a higher rate of nasal congestion, nor a harsher clinical course, in allergic children[61]. Sedaghat et al.[53, 62] observed that pediatric patients with AR and CRS seem to have the same aeroallergen sensitivity profile compared to the general pediatric population with AR. Furthermore, the authors did not find a positive association between the number of aeroallergen sensitivities or the presence of atopic comorbidities with the subsequent development of CRS, suggesting that the severity of atopy alone may not be positively predictive of CRS development. These articles were not included in the qualitative analyses due to the type of article.

2.1.3 Impact of allergy on outcome of chronic rhinosinusitis treatment.

Ramadan and Hinerman[63], in a retrospective study, noted that children with AR underwent to ESS do not have a poorer outcome respect non allergic one. Nevertheless, children with AR who were on immunotherapy before surgery had an 84% success rate compared with 62% for those children with AR who were not treated (p = 0.022). Accordingly, Nathan et al.[64] using the Sinusitis Outcomes Questionnaire (SOQ), demonstrated that immunotherapy was an effective treatment for patients with sinus disease and AR in both children and adults.

About surgery outcomes, Kim et al.[65] and El Sharkawy et al.[66] observed that functional endoscopic sinus surgery in children with CRS and AR does not provide significantly different results compared to children without AR, which is similar to what has been reported in adults[67]. On the contrary, in a study by Lee et al.[68], a significantly greater chance of protracted mucopurulent discharge after FESS was registered in patients with AR. The authors assumed that the inflammatory process of nasal allergy, which led to the development of CRS, probably impaired the post-operative wound healing by mucosal congestion, poor-functioning muco-ciliary clearance and recurrent sneezing that placed pressure on the denuded mucosa. An analogous conclusion was made by Wu et al.[69] who demonstrated that pediatric patients with positive aeroallergen tests had higher rates of CRS recurrence after ESS and required revision surgery.

2.2 Allergic fungal sinusitis (AFS) in children.

AFRS is also present in the paediatric age group and it should be considered as a differential in children presenting with nasal polyposis along with the other causes like ciliary dysmotility disorders and cystic fibrosis[70]. There is paucity of data in literature regarding nature, clinical course and its recurrence in children and it was not possible to perform a qualitative analysis. Patro et al.[71] in a single centre prospective study compared features of AFRS in children to adults. The authors concluded that AFRS was more aggressive in children with increased fungal load when compared to adults. The serum IgE levels were also found to be significantly higher in paediatric group, suggesting a higher fungal load, with increased sensitivity to fungal antigen in children. Typically, AFRS in children was less responsive to treatment, with increased recurrence rates.

CONCLUSIONS.

AR is a common disease in childhood in industrialized countries and it has a major impact on quality of life and health care resources. Improving the understanding of the pathophysiology of allergy and relationship with its comorbidities is important to correctly develop timed preventive measures as well as perform adequate monitoring and treatment of children with rhinitis. The correct management of allergic diseases can, in fact, decrease the inflammatory response and most likely lead to better control of comorbidities.

Our qualitative analyses demonstrated that there is clear evidence from the lab of a link between allergy and an overall impairment of mechanical and immunological defense function of nasal mucosa against viruses.

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Clinical studies support the hypothesis of a positive association between allergy and viral acute rhinosinusitis/URTI, and only low-quality retrospective studies reached conflicting results. Proof of this is the existence of high-quality investigations showing that anti-allergy treatments may significantly decrease the number and severity of URTI including common colds. We did not find any articles investigating specifically the link between allergy and upper airway involvement by the new coronavirus in children.

Current experimental and clinical experience does not support an etiological link between allergy and post viral rhinosinusitis, ABRS and RARS. At the moment anti-allergy treatments are not advised in these phenotypes even though well design high quality studies are required to improve our knowledge in this field reaching firm conclusions.

Despite the growing knowledge related to allergy and chronic rhinosinusitis in children, it is not yet clear whether AR may promote CRS or if they only share a common pathway of pathogenesis. Even if AR has been positively associated with CRS in several experimental and clinical studies in children, conflicting results have also been reported, probably because of discrepancies in definitions of the disease processes for both CRS and AR and allergy testing methodologies. Researchers have used a variety of techniques to document the presence of sinusitis, such as patient surveys, radiography, CT scan, rhinoscopy, and routine physical examination, and, therefore, the results may not reflect homogeneous populations. In addition, experimental studies and radiological assessment are often prevented by local ethical committees in the pediatric population, for comprehensible reasons. Furthermore, the evidence supports the hypothesis that CRS in children over the age of 13 seems to be more frequently associated with eosinophilic inflammation, whereas in younger patients with CRS neutrophilic inflammation is observed more often[10,11]. We did not find investigations analyzing the impact of allergy on CRS based on age, and we believe that more data from large epidemiological studies using explicit criteria is needed.

Although there is no proof of causation, several studies suggested that evaluation of underlying allergies in CRS children is equally recommended, at least to exclude allergy as a concomitant disease and to improve control of symptoms avoiding exposure to known allergens and promoting allergy therapies. Future studies are needed to confirm that anti-allergy treatment may improve outcomes of endoscopic sinus surgery for CRS in children.

We summarized in a practical algorithm our conclusions per each phenotypes of rhinosinusitis in order to elucidate when prompt accurate diagnosis and treatment of allergy is recommended (Figure 2).

IMPACT STATEMENT.

The unprecedented pandemic by COVID-19 lead to a special attention to vulnerability of children. Clinical and experimental studies suggest a link between allergy and viral acute RS, whereas any correlation may be established with bacterial acute RS. Anti-allergy treatment may prevent and reduce severity of viral acute RS even though any articles investigated specifically the link between allergy and upper airway involvement by the new coronavirus in children. Nevertheless, in this particular era a regular treatment plan should be adopted in allergic children not only to reduce the risk of viral acute RS but also because symptoms may considerably overlap. Finally, although there is no proof of causation of allergy in chronic RS children, anti-allergy treatment might improve outcomes of its specific treatment.

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Table I. Laboratory evidence linking allergy to impairment of mechanical and immunological function of epithelial barrier.

Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection
Author Year (ref)	No. of cases	Experimental models	Methods	Relevant results	Association (Level of evidence)
Waltl et al. 2018 (12)	N=20	Cultured human cells from inferior nasal turbinate.	Impedance-based measurement of respiratory epithelial barrier function after the exposure to different concentrations of House dust mites (HDM) extract.	Dose dependent decrease of barrier function, alteration of morphology and thickness of the epithelium, decrease of ciliary beat frequency and tight junction expression, facilitating pathogen permeability.	Yes (Level V)

Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection
Steelant et al. 2016 (13)	N=25. 9 pz and 16 controls	Cultures of primary nasal epithelial cells of patients with HDM-induced allergic rhinitis (AR) and controls.	Measurement of transepithelial resistance and passage of fluorescein isothiocyanate-dextran 4 (FD4), quantitative PCR of tight junction expression and effects of IL-4, IFN-γ, and fluticasone propionate (FP).	AR have increased FD4 permeability and reduced occludin and zonula occludens-1 expression; in vitro IL-4 decreased transepithelial resistance and increased FD4 permeability, whereas IFN-γ had no effect. FP prevented IL-4-induced barrier dysfunction.	Yes (Level V)
Steelant et al. 2018 (14)	N= 9 allergic rhinitis; 6 idiopathic rhinitis; 10 controls.	Cultures of primary nasal epithelial cells from healthy control exposed to nasal secretions of allergic vs non-allergic patients.	Measurement of transepithelial electrical resistance, paracellular flux of fluorescein isothiocyanate-dextran 4 and mRNA expression of tight junctions.	Histamine and nasal secretions from AR, but not from idiopathic rhinitis patients, rapidly decrease in trans-tissue resistance. Pre-treatment with histamine receptor-1 antagonist, azelastine, prevented the early effect of nasal secretions of AR patients on epithelial integrity.	Yes (Level V)

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Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection
Głobińska 2017 (18)	N=19 (8 AR and 11 healthy controls).	Cultured nasal epithelial cells (NECs) exposed to parainfluenza virus type 3 (PIV3), rhinovirus 1B (RV1B) and intracellular TLR agonists.	Interferon (IFN)-k1, IFN-a, IFN-b released into the cell culture supernatants was assessed at 8, 24 and 48 h upon infection; mRNA levels of IFNs, RANTES, were determined using real-time polymerase chain reaction (RT-PCR).	PIV3 infection induced significantly less IFN-k1 (both protein and mRNA) in NECs from AR compared to healthy controls. IFN-b mRNA expression and RANTES protein release tended to be smaller in AR compared controls cells in response to both viruses.	Yes (Level V)
Fenoglio et al. 2008 (19)	N=41 AR patients	Peripheral blood mononuclear cells (PBMC) producing IFN-in vitro.	IFN-γ-specific producing cells were stimulated with Phyto-haemagglutinin (PHA), causal pollen, and House Dust Mite (HDM). IFN-γ production was assessed by cytokine ELISPOT.	IFN-γ production of PBMC stimulated by specific pollen was significantly lower than IFN-γ production of PBMC stimulated by HDM. IFN-γ production of PBMC stimulated by specific pollen was significantly lower than IFN-γ production of PBMC stimulated by PHA.	Yes (Level V)

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Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection	Evidence from the lab linking allergy to increased risk of epithelial cells viral infection
Teach et al. 2015 (20)	N=478 children (10.2±2.93 yr).	Peripheral blood mononuclear cell cultures incubated ex-vivo with rhinovirus.	Measuring INF-α in supernatants of PBMCs cultures obtained from a subset of subjects (n = 87) incubated ex-vivo with rhinovirusin patients treated or not with Omalizumab.	The group treated with anti-IgE had improved INF-α production after virus infection suggesting restoring of the impaired interferon response and increasing antiviral immunity and suggesting that anti-IgE may prevent upper and lower respiratory infections and asthma exacerbations	Yes (Level V)

Table II: Articles investigating clinical association between allergy and upper respiratory infections.

Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections
Author Year (ref)	Type of article	No. of cases (mean age)	Methods	Relevant results	Association (Level of evidence)
Karevold et al. 2006 (21)	Cross-sectional survey.	N= 5125 (10 yr).	Assess co-morbidity and risk factors for recurrent upper and lower respiratory infections.	Atopic disease was a constitutional risk factor, for upper and lower airway infections.	Yes (Level IV)

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Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections
Ciprandi et al. 2009 (22)	Prospective study.	N=117 (4.02 ± 1.0yr); 46 allergic.	Evaluate the number and duration of respiratory infections (RI) in allergic and non-allergic children.	Allergic children showed a significantly higher number (mean 1.26 +/- 0.73) and longer duration of RI (8.92 days) in comparison with non-allergic group (0.94 +/- 1.37 and 4.85 days).	Yes (Level II)
Kværner et al. 1996 (23)	Retrospective analysis.	N= 7992 (mean age not known)	Estimate comorbidity between ear infections, tonsillitis, sinusitis and related childhood diseases	The correlation between the infectious and atopic diseases were weak.	Inconclusive (Level IV)
Sütçü et al. 2016 (24)	Retrospective analysis.	N= 507 children (46, range 4-190, months)	Evaluate children presenting with the complaint of recurrent infections and to determine the possible predictive factors.	Atopic children had longer episodes of recurrent URTI compared to controls; however, the number of episodes per year was not significantly different.	No (Level IV)
Role of anti-allergy treatment in preventing upper respiratory infections.	Role of anti-allergy treatment in preventing upper respiratory infections.	Role of anti-allergy treatment in preventing upper respiratory infections.	Role of anti-allergy treatment in preventing upper respiratory infections.	Role of anti-allergy treatment in preventing upper respiratory infections.	Role of anti-allergy treatment in preventing upper respiratory infections.

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Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections
Ciprandi 1999 (22)	Double-blind and placebo-controlled study.	N= 20 children with allergy; 10 terfendine group (8.5±3 yr); 10 placebo (7.9±2.7 yr).	Continuous terfenadine (1 mg/kg per body weight per day) vs placebo for 1 year. Outcome: Symptoms; inflammatory cells and ICAM-1 measured by nasal scraping.	Terfenadine treatment reduce ICAM-1 expression on nasal epithelial cells; children treated with terfenadine had significantly fewer extra visits and school absences than the placebo group.	Yes (Level I)
Fasce 1996 (16)	Double-blind, placebo controlled randomized study.	N= 20 children (5-14 years old) with mite allergy.	Cetirizine vs placebo for 15 days. Nasal scrapings were performed to evaluate inflammatory cell infiltration and ICAM-I expression on epithelial cells.	Cetirizine-treated children showed a significant reduction (or even total absence) of ICAM-I expression on epithelial cells (p=0.002) and a reduction trend in inflammatory cell counts compared with placebo	Yes (Level I)
Barebri et al 2015 (27)	Prospective case control observational stydy, not-randomised.	N=40 HDM allergic children (9.3 yr)	Patients were subdivided in 2 groups: 20 treated by symptomatic drugs and 20 by high-dose HDM-SLIT.	SLIT-treated children had significantly (p = 0.01) less RI episodes (3.5) than control group (5.45).	Yes (Level II)

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Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections	Clinical evidence linking allergy to risk of upper respiratory tract infections
Barberi 2018 (26)	Retrospective analysis.	N= 33 HDM allergic children (9.3 yr).	Investigate whether 3 year high-dose HDM-SLIT affects respiratory infections in children with allergic rhinitis.	SLIT-treated children had significantly fewer RI episodes than symptomatically treated children. In addition, they had less fever and took fewer medications, such as antibiotics and antipyretics.	Yes (Level IV)

HDM: house dust mites; SLIT: sub-lingual immunotherapy; URTI: upper respiratory tract infections; RI: respiratory infections. RI: respiratory infections

Table III Evidence from the lab linking allergy to CRS in children.

Laboratory evidence linking allergy to risk of CRS	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*
Author Year ( ) ref	No. of cases	Experimental models	Methods	Relevant results	Association (Level of evidence)
Chawes, 2011 (45)	N= 411 children with AR, non AR and healthy controls (6 yr)	Nasal airway patency was assessed by acoustic rhinometry.	Acoustic rhinometry was performed twice in the child's 6th year of life, with or without allergy. Nasal eosinophilia was assessed by nasal scraping.	Nasal eosinophilia correlated with irreversible nasal airway obstruction, in allergic children already at age 6 years. No change in nasal airway patency were observed in non-allergic rhinitis.	Yes (Level III)

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Laboratory evidence linking allergy to risk of CRS	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*	*Laboratory evidence linking allergy to risk of CRS*
Blair et al. 2001 (46)	N/A	Mouse sensitized to ovalbumin by intraperitoneal injection.	Sinuses of the mouse were infected by S. Pneumoniae, with or without concomitant administration of ovalbumin to induce or not aller-gic inflammation.	Mice with allergic sino-nasal inflammation had significantly more bacteria and significantly more inflammation (as indicated by neutrophil, eosinophil, and mononuclear influx) into the sinus respect the non-allergic ones.	Yes (Level V)
Shin et al. 2015 (47)	N= 36 CRS responders vs 22 CRS non-responders, 22 healthy controls. (age<15yr)	Serum analyses.	Skin prick tests were performed along with serum total IgE, total eosinophil count (TEC), serum eosinophil cationic protein (ECP) level, and ImmunoCAP analysis for common allergens.	TEC, ECP, and total IgE levels were significantly higher in the non-responder group than in the responder and control groups.	Yes (Level III)
Mikolajczyk et al. 2019 (48)	N= 842 AR children and 96 controls.	%EOSns. MCT.	All patients underwent saccharin and skin prick tests, nasal smear eosinophilia, total and specific IgE serum concentration and MCT measurement.	Nasal MCT was significantly longer in AR patients than controls. %EOSns were significantly higher in patients than controls. A weak, but significant correlation was observed between %EOSns and MCT.	Yes (Level III)

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Laboratory evidence linking allergy to risk of CRS	Laboratory evidence linking allergy to risk of CRS	Laboratory evidence linking allergy to risk of CRS	Laboratory evidence linking allergy to risk of CRS	Laboratory evidence linking allergy to risk of CRS	Laboratory evidence linking allergy to risk of CRS
Brożek-Madry et al. 2012 (49)	N= 64 patients with chronic rhinosinusitis without polyps and 30 controls (age 5-18 yr).	Epithelial cultures (middle meatal cells).	Middle meatal culture and cytological examination from the inferior nasal concha and middle meatus.	The most common strains of bacteria found in patients with CRS were associated with a higher percentage of eosinophils in cytology and high prevalence in atopic patients.	Yes (Level V)

AR: allergic rhinitis; CRS: chronic rhinosinusitis; MCT: mucociliary transport time: %EOSns: percentage of eosinophils in nasal smear.

Table IV: Clinical evidence linking allergy to CRS in children.

Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children
Author Year ( ) ref	Type of article	No. of cases (mean age)	Methods	Relevant results	Association (Level of evidence)
Sedaghat et al. 2014 (57)	Retrospective analysis.	N= 4044 children with CRS (8.9 yr).	Retrospective review of children diagnosed as uncomplicated CRS by an otolaryngology or allergy office evaluation	Comorbidities observed in CRS children were primary ciliary dyskinesia (0.2%), cystic fibrosis (4.1%), immunologic disorder (12.3%) and AR (26.9%).	Inconclusive (Level IV)

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Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children
Choi et al. 2012 (34)	Prospective study.	N=296 (<13yr) with RS	To evaluate predisposing factors for chronic and recurrent rhinosinusitis (RS).	The prevalence of AR, atopy, and asthma were significantly higher in patients with CRS and recurrent RS than those with acute and subacute RS.	Yes (Level II)
Anamika et al. 2019 (58)	Cross-sectional study.	N=110 children with CRS (7-18yr).	To determine atopic profile of children with CRS and impact of atopic status on disease severity and quality of life.	Positive skin prick test was present in 52.7% of patients. Atopic CRS had a significant higher mean Lund-Mackay endoscopic score and symptoms scores than non-atopic ones.	Yes (Level IV)
Huang 2000 (59)	Prospective observational study	N= 413 RA children. (3-15 yr).	To evaluate mold allergy as risk factor for sinusitis. The authors compared 215 PAR to 198 SAR.	The prevalence of sinusitis was significantly higher among patients with PAR than among those with SAR regardless of age or season; patients with mold allergy PAR had a higher risk than those with non-mold allergy.	Yes (Level II)

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Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children
Leo et al. 2007 (60)	Cross-sectional study	N=351 children with CRS (5.23 ± 2.11 yr)	CRS underwent allergen sensitization work-up by skin prick test with common inhalant allergens and total IgE measurement.	Prevalence of sensitization to aeroallergens in children with CRS is comparable with that of the general pediatric population.	No (Level IV)
Clinical evidence linking allergy to outcome of CRS treatments in children Nathan et al. 2004 (64)	Clinical evidence linking allergy to outcome of CRS treatments in children Prospective observational study	Clinical evidence linking allergy to outcome of CRS treatments in children N= 114 RA and CRS (children and adult)	Clinical evidence linking allergy to outcome of CRS treatments in children Patients were surveyed for global symptoms and specific symptoms related to the nose, sinuses, eyes, and chest with the SOQ	Clinical evidence linking allergy to outcome of CRS treatments in children Immunotherapy is an effective treatment for patients with sinus disease and allergic rhinitis.	Clinical evidence linking allergy to outcome of CRS treatments in children Yes (Level II)
Ramadan, & Hinerman 2006 (63)	Prospective observational study.	N= 141 patients who underwent ESS (7 yr)	To evaluate outcome of ESS at 1 year after the operation.	Children with AR who were on treatment before surgery had an 84% success rate compared with 62% for those children with non-treated AR by immunotherapy.	Yes (Level II)
Kim et al. 2005 (65)	Retrospective observational study.	N=97 patients (age range: 5—15 years)	Retrospective analysis of long-term success rates of ESS respect to several predisposing factors.	Multivariate logistic regression analysis allergy was not correlated to poor outcomes after pediatric ESS	No (Level IV)

Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children	Clinical evidence linking allergy to risk of CRS in children
El Sharkawy 2012 (66)	Prospective observational study.	N=87 children (45 with nasal allergy) (age[?]14)	To assess predictive factors of outcome after ESS.	The success rate in CRS with nasal allergy was 87.5%, and in CRS without nasal allergy was 85.7%.	No (Level II)
Lee et al. 2009 (68)	Retrospective analysis	N=53 children who underwent FESS (age<18yr)	To investigate factors leading to protracted nasal discharge after pediatric endoscopic sinus surgery.	Blood eosinophil count did not differ significantly between the "protracted" and the "resolved" groups. On the other hand, history of allergic rhinitis was more frequently observed in the "protracted" group.	Yes (Level IV)
Wu et al. 2019 (69)	Retrospective analysis	N=188 children ESS for CRS.	To evaluate prognostic factors related to revision surgery after ESS.	Patients with positive aeroallergen tests had higher rates of CRS recurrence after ESS and required revision surgery.	Yes (Level IV)

CRS: chronic rhinosinusitis; AR: allergic rhinitis; PAR: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; SOQ: Sinusitis Outcome Questionnaire; ESS: endoscopic sinus surgery; FESS: functional endoscopic sinus surgery.

Figure 1. Flow chart of articles selection.
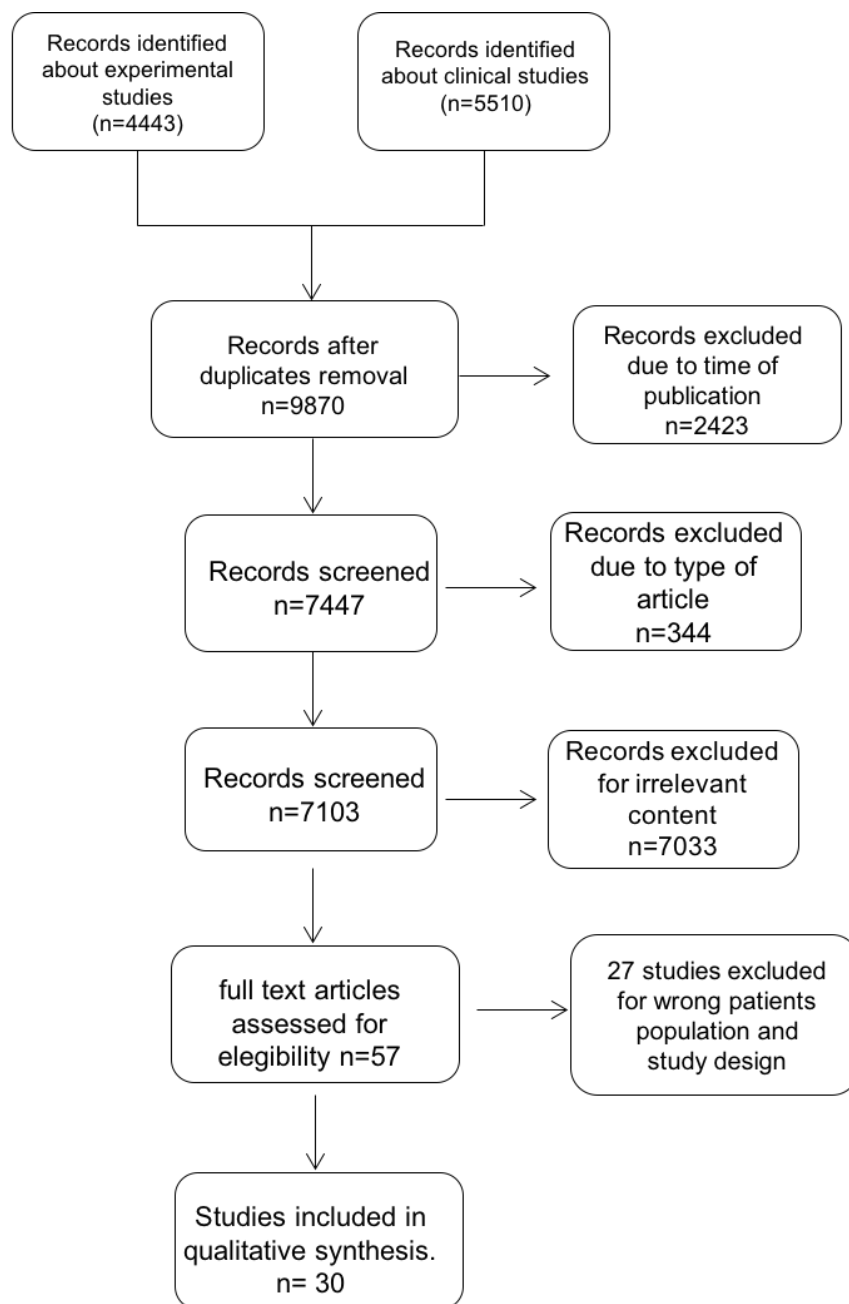
Figure 2: Practical algorithm based on different phenotypes of rhinosinusitis in children.

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                              RHINOSINUSITIS
                                in children

                              Accurate phenotyping
                              of rhinosinusitis is
                                recommended


              ARS                             CRS            AFS


 Viral ARS      Post viral ABRS  ABRS  RARS
including URTI


Experimental and clinical                         Although no proof of      it should be considered
evidence support a link                           causation, allergy        as a differential
with allergy as                                   evaluation is             diagnosis in children
predisposing factor        Heterogeneity and paucity of studies did   recommended to          with nasal polyposis
                           not allow a qualitative analyses.          exclude it as a         Mold allergy should be
                           At the moment no evidence supporting a     concomitant disease and investigated
Anti allergy treatments    link between this phenotypes and allergy   to improve control of
may prevent frequencies    Future studies are required.               symptoms. Future
and reduce severity of                                                studies are required.
episodes.
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┌─────────────────────┐   ┌─────────────────────┐
│ Records identified  │   │ Records identified  │
│ about experimental  │   │ about clinical      │
│ studies             │   │ studies             │
│ (n=4443)            │   │ (n=5510)            │
└─────────────────────┘   └─────────────────────┘
              │                   │
              └─────────┬─────────┘
                        ▼
          ┌──────────────────────┐      ┌──────────────────────┐
          │ Records after        │      │ Records excluded     │
          │ duplicates removal   │─────▶│ due to time of       │
          │ n=9870               │      │ publication          │
          └──────────────────────┘      │ n=2423               │
                        │               └──────────────────────┘
                        ▼
          ┌──────────────────────┐      ┌──────────────────────┐
          │ Records screened     │      │ Records excluded     │
          │ n=7447               │─────▶│ due to type of       │
          └──────────────────────┘      │ article              │
                        │               │ n=344                │
                        ▼               └──────────────────────┘
          ┌──────────────────────┐      ┌──────────────────────┐
          │ Records screened     │      │ Records excluded     │
          │ n=7103               │─────▶│ for irrelevant       │
          └──────────────────────┘      │ content              │
                        │               │ n=7033               │
                        ▼               └──────────────────────┘
          ┌──────────────────────┐      ┌──────────────────────┐
          │ full text articles   │      │ 27 studies excluded  │
          │ assessed for         │─────▶│ for wrong patients   │
          │ elegibility n=57     │      │ population and       │
          └──────────────────────┘      │ study design         │
                        │               └──────────────────────┘
                        ▼
          ┌──────────────────────┐
          │ Studies included in  │
          │ qualitative synthesis.│
          │ n= 30                │
          └──────────────────────┘
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RHINOSINUSITIS
in children

Accurate phenotyping
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ARS

CRS

AFS

Viral ARS
including URTI

Post viral ABRS

ABRS

RARS

Experimental and clinical
evidence support a link
with allergy as
predisposing factor

Anti allergy treatments
may prevent frequencies
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it should be considered
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diagnosis in children
with nasal polyposis
Mold allergy should be
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