#01/2021
ISSN 2299-1247

JHPOR | Journal of Health Policy & Outcomes Research

Challenges and opportunities in the treatment of chronic rhinosinusitis in children

DOI:10.7365/JHPOR.2021.2.4

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Keywords:

sinusitis, rhinitis, child, adolescent, otolaryngology, microbiota, macrolides, nasal mucosa

How to cite this article?
Standyło A., Obuchowska A., Horoch A., Mielnik-Niedzielska G., Niedzielski A., Challenges and opportunities in the treatment of chronic rhinosinusitis in children. J Health Policy Outcomes Res [Internet]. 2021 [cited YYYY Mon DD];1. Available from: https://www.jhpor.com/article/2271-challenges-and-opportunities-in-the-treatment-of-chronic-rhinosinusitis-in-children

contributed: 2021-07-21 final review: 2021-08-13 published: 2021-08-29

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Abstract

Paediatric chronic rhinosinusitis (PCRS) is a common disease in children. It is defined as continuing inflammation of the nasal cavity and sinuses for ≥12 weeks. Because of the compound aetiology and pathophysiology of this disease in children, it is extremely important for the physician to consider the differential diagnosis before planning treatment. The aim of the review was to present the guidelines from The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) and promising treatment options of CRS in the paediatric population.

The authors of the guidelines proposed a new division of chronic sinusitis (CRS). Chronic sinusitis has a greater impact on deteriorating the quality of life of patients than acute sinusitis. CRS is a syndrome with a multifactorial aetiology, resulting from an abnormal interaction between particular environmental factors and the host's immune system. The mucosa is chronically penetrated by the inflammatory process, which in many cases leads to tissue remodelling and clinical symptoms. EPOS 2020 recommendations are based on the use of proper nasal hygiene, sinus saline irrigations and topical corticosteroids. Surgical intervention is considered for patients with CRS who have failed appropriate medical therapy. However, there are new promising therapies on the horizon.

The EPOS 2020 guidelines signaled the impact of immunomodulation on the development of the disease. In addition to the standard therapy recommended by EPOS 2020, new therapeutic options, such as low-dose macrolide (LDM) therapy and biological treatment, that may have a potential impact on improving CRS treatment in children, should be investigated.

Introduction and objective

Paediatric chronic rhinosinusitis (PCRS) is a common disease in children under 18 year old and is defined as continuing inflammation of the nasal cavity and sinuses for ≥12 weeks [1]. PCRS differs significantly from adult chronic rhinosinusitis (CRS) in terms of clinical features.

An important symptom in children is chronic cough.[2]

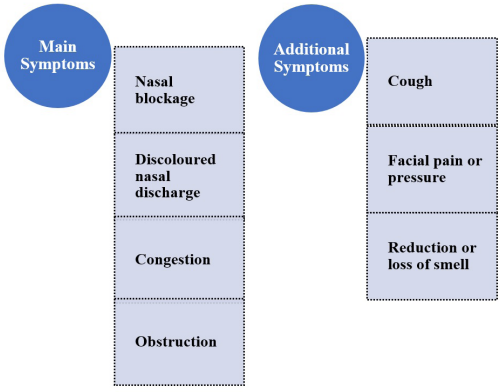

Figure 1. Basic differences in the pharmacokinetics of anakinra and canakinumab.

It is estimated that the incidence of CRS in children and adolescents under 18 years old is up to 4%.[1] Paediatric CRS is associated with a high financial and healthcare burden due to its prevalence in the population. Repeated visits to the clinic lead to the loss school days and parents' days off. CRS also affects negatively quality of life and learning ability.[3] Because of the compound aetiology and pathophysiology of this disease in children, it is extremely important for the physician to consider the differential diagnosis before planning treatment. Depending on age, specific factors that contribute to sinusitis are distinguished. In younger children it is adenoiditis, and in older children it is allergic rhinitis.[4] Inflammation, mucociliary dysfunction and changes in the microbial environment are causing the disease.[1] Recent work has focused on the nasal microbiome and its role in infection and inflammation.[2,5,6]

In this review, guidelines from The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) and recent literature reports from the Medline and Scopus databases were analysed. It pays a special attention to new promising treatment options of CRS in the paediatric population. The articles present the most up-todate guidelines for symptomatology, diagnosis and treatment in children with chronic sinusitis.

Description of the state of knowledge

The authors of the guidelines proposed a new division of chronic sinusitis (CRS) which is presented on Figure 2 and Figure 3.

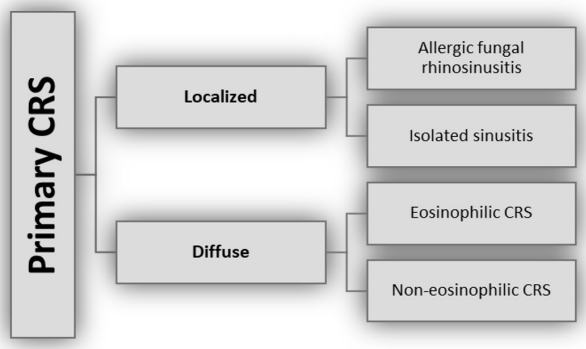

Figure 2. The new division of chronic sinusitis (CRS) - Primary CRS.

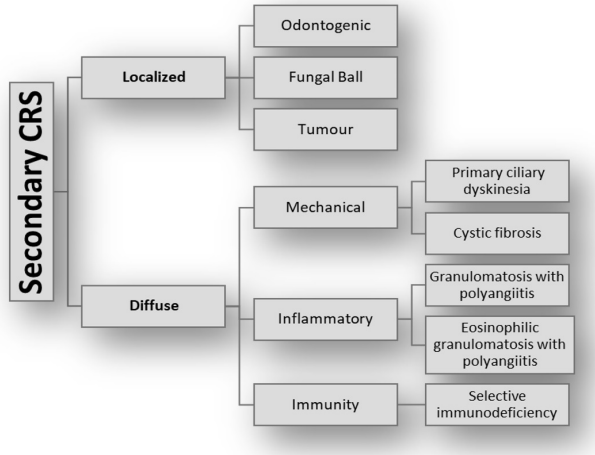

Figure 3. The new division of chronic sinusitis (CRS) - Secondary CRS.

In EPOS 2020, no changes were made to the definition of severity, or to the criteria for classifying acute and chronic sinusitis.

Chronic sinusitis has a greater impact on deteriorating the quality of life of patients than acute sinusitis. The impact of CRS on the global quality of life and social functioning is greater than in the course of angina or chronic heart failure.[1] The most insufferable and common symptoms in CRS with polyps are nasal obstruction and disturbances in the sense of smell and taste. In CRS without polyps, there is also nasal obstruction, facial pain, and disturbed sense of smell and taste.[7,8]

CRS is a syndrome with a multifactorial aetiology, resulting from an abnormal interaction between particular environmental factors and the host's immune system. This allowed for a different approach to CRS therapy. It is known that both the nasal cavities and the sinuses are not sterile: the colonization of the nasal cavities and paranasal sinuses by viruses, bacteria and fungi begins at birth. In healthy humans, the mucosa is a barrier that modulates the host's immune system, promotes tolerance, and prevents and reduces inflammation. In patients with CRS, this barrier is chronically penetrated by the inflammatory process, which in many cases leads to tissue remodelling and clinical symptoms.[1] Scientists focused on identifying the molecular pathways and endotypes that were triggered. After pathogens penetrate the mucosal barrier, an immune response occurs, characterized by a cellular and cytokine response targeting one of the three types of pathogens: viruses (type 1), parasites (type 2) or extracellular bacteria and fungi (type 3). All these reactions conclude in the elimination of pathogens and the restoration of the integrity of the mucosa.[1] In CRS, mucosal penetration persists, resulting in a chronic inflammatory response. In type 2 inflammation, the cytokines interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13) are released, and eosinophils and mast cells are recruited and activated. Studies have shown that patients with endotype 2 are more resistant to current therapies and have frequent relapses.[1]

Remodelling of the sinonasal tissue in CRS mainly consists in the formation of polyps, goblet cell hyperplasia and damage to the epithelial barrier. These changes may be responsible for many or most of the symptoms and a high rate of treatment failure. The mainstay of treatment of patients with generalized CRS is topical glucocorticosteroid (GCS) therapy and rinsing of the nasal cavities with saline.[1]

Exacerbation of chronic paranasal sinusitis (CRS) is defined as the severity of CRS symptoms, which returns to the baseline state as a result of glucocorticoid therapy and / or antibiotic therapy. The precise aetiology of CRS exacerbation is still unexplained, but it is believed to be multifactorial. The major factor is the altered balance of the microbiota, not the single pathogen leading to the inflammatory response in the host. On the other hand, viral infections may be a likely cause of CRS exacerbations, especially as there is growing evidence that rhinovirus infection can lead to eosinophilic inflammation. Focusing on the prevention and appropriate treatment of viral infections may be more effective than treating secondary infections with antibiotics or treating eosinophilia with glucocorticoids. There is still a lack of scientific evidence that would decide on the optimal treatment of CRS exacerbation. Despite this fact, GCS and antibiotics remain the basis for the treatment of CRS exacerbations, although their role in therapy has not been confirmed in the literature.[1]

Upper respiratory tract infections (URTI) are a common cause of medical visits for paediatric patients, with 5–13% of these URTIs progressing to acute bacterial sinusitis, some of which progress to PCRS. There are many factors that contribute to the development of sinusitis. The most frequently mentioned are the adenoids, impairment in mucociliary clearance (e.g., primary ciliary dyskinesia, and cystic fibrosis), and anatomic abnormalities of the sinuses. Adenoids influences the development of PCRS especially in children under 12 years of age.[9] Wherefore, adenoidectomy is one of the most frequently performed procedures, but its effectiveness has not been demonstrated in children over 13 years of age.[10,11] The adenoid tissue is a reservoir of bacteria and causes posterior nasal obstruction, which causes an impairment of the mucociliary clearance of the sinus cavities.[9] Bacterial biofilms have been shown to cover the mucosa of the tonsils, tonsils and sinuses. The microbiome of adult and paediatric patients is different.[2] The most common pathogenic organisms identified in the adenoids include Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, and group A streptococci, Corynebacterium spp.[2] The presence of biofilm can cause incomplete penetration of antibiotics and result in a lack of clinical improvement despite frequent courses of antibiotics.[9]

Diagnostics is based on several tests. It is important to observe major clinical signs during physical examination to determine if CRS is suspected. The EPOS guidelines recommend nasal endoscopy as a preliminary objective method to aid in the recognition of CRS.[1,12] Another modality to visualize the CRS is computed tomography (CT). CT can support navigation during surgical procedures and provide high sensitivity for mucosal inflammation.[4] CT is the gold standard for imaging when establishing a PCRS diagnosis or preparing for sinus surgery, particularly a non-contrasted CT with axial, coronal, and sagittal views. CT is recommended in patients with PCRS in whom conservative treatment and / or adenoidectomy did not control the symptoms of the disease and in patients with suspected complications.[1,9] Nevertheless, there are some limitations that must be taken into consideration. There are reports of an increased risk of brain tumour (2-3 head CTs) and leukaemia (5-10 brain CTs) in children in association with radiation exposure during CT.[4,7] Magnetic Resonance Imaging (MRI) is another medical imaging technique. The lack of exposure to radiation makes MRI a safer choice in the diagnosis of CRS. The downside is that MRI does not reveal bone details that are often required when considering surgical interventions.[13] The use of X-rays for PCRS is limited.[9]

Topical corticosteroids and saline lavage are considered the first line of therapy in the treatment of Paediatric CRS. Studies have shown that topical nasal steroid sprays and daily nasal irrigation with a saline solution are beneficial medical treatments.[10] Due to the lack of evidence, the use of antibiotics is not recommended. Surgical intervention should be considered in patients with unsuccessful conservative treatment.[1]

Surgical treatment is reserved for cases, where pharmacological treatment has failed.[14] However, there is no general agreement on the surgical treatment of CRS in paediatric patients. EPOS 2020 suggest that adenoidectomy is considered first-line in children under 12 years of age. Adenoidectomies with or without sinus irrigation appear to be the safest.[1,15] Functional endoscopic sinus surgery (FESS) should only be considered in case of failure of pharmacological therapy and adenoidectomy. FESS also should be considered in patients with disorders in mucociliary function and without adenoid hypertrophy.[1,14]

Currently the success rate of medical management of CRS is approximately 50%.[16]

Hard-to-treat CRS is called refractory CRS and occurs when all treatment options have failed. It occurs in patients who have persistent symptoms despite recommended medical or surgical treatment. Patients suffering from difficult-to-treat rhinosinusitis should be considered patients who do not achieve an acceptable level of symptom control despite appropriate surgical treatment, intranasal glucocorticoid treatment and despite the use of two short antibiotic treatments or oral glucocorticoid treatments during the last year.[1]

Refractory CRS is common in paediatric patients, thus It is essential to understand the inflammatory pattern of paediatric CRS to control the refractory disease.[17]

The majority of treatment-resistant CRS in children is associated with neutrophilic inflammation with elevated levels of interferon-γ, transforming growth factor β (TGF-β), interleukin-17 (IL-17), myeloperoxidase, interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-1β (IL-1β).[17] Long-term low-dose macrolide (LDM) therapy suppresses production of pro-inflammatory cytokines such as IL-8 and TNF-α, moreover LDM modulates mucus synthesis and secretion resulting in effective mucus clearance.[17] Unfortunately, there is no guideline or consensus that applies to children, to evaluate the clinical efficacy of LDM in the treatment of paediatric CRS and it has not been mentioned in EPOS 2020 guidelines. However, Seresirikachorn et al. investigated the effects of LDMs on paediatric CRS patients who did not respond to the standard treatment. In their study paediatric patients received LDM therapy with concomitant nasal steroid spray intervention.[17] They propose, that LDM therapy should be administered with half of the full dose of the antibacterial agent for more than 3 months and could be second-line treatment for children with CRS. This option should be considered prior to adenoidectomy, sinus aspiration, and endoscopic sinus surgery.[17]

Another promising modality for treatment of CRS in paediatric patients with refractory conditions are biologics. Newly developed targeted and specific therapies such as biologics may be treatment strategies that can target resistant CRS [16]. Patients with refractory CRS and who require multiple doses of corticosteroids are the most evident candidates for the use of biologics.[16] By using targeted therapy, inflammation is reduced and symptom control is ensured with fewer side effects. Consequently, there is a reduced need for multiple corticosteroid use.[18,19]

In 2019, Dupilumab (anti-IL-4R alpha Immunoglobulin) was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment in adults with CRS type 2. Biological treatment criteria include patients who meet at least three of the following criteria: CRS type 2, systemic glucocorticoid requirement, deterioration in quality of life, anosmia, concomitant asthma.[1,20]

However, currently the use of biological drugs is restricted to patients with uncontrolled severe asthma and as a therapeutic option in patients with CRS refractors when drugs and surgery have failed.[16,18]

The current EPOS 2020 recommendations are briefly provided in this overview. They can be utilized in clinical practice on a daily basis. It's worth noting that research into chronic paranasal sinusitis in children and the search for causes of the disease's onset could help to improve the diagnostic and therapeutic procedure, as well as reduce treatment costs.

The impact of the EPOS 2020 guidelines on health policy and national guidelines will enable patients to be diagnosed and treated using evidence-based medicine. By propagating the recommendations among General Practitioners, CRS could be diagnosed earlier and treatment suited to the patient can be implemented more effectively. The development of new treatment methods that would significantly influence the treatment of Paediatric CRS should also be carefully monitored.

Conclusion

Despite the significant increase in the number of publications in recent years, many clinical questions remain unanswered. Immunomodulation is a common term used in the EPOS 2020 guidelines. It means all medical interventions aimed at modifying the immune response. Biologics and LDM are effective in immunomodulation, therefore further studies are needed to assess their impact on the treatment of Paediatric CRS. Research into microbiota dysfunction and its impact on CRS development may explain the causal relationship between microbiota imbalance and the inflammatory response in the host. There is still no scientific evidence to support the optimal treatment of CRS exacerbation. Social and environmental factors, especially exposure to tobacco smoke, are becoming increasingly important in primary prevention and the effects of global warming and industrial pollution should be carefully monitored.

Conflicts of Interest

The authors declare no conflict of interest.

Funding Information

This research did not receive any specific grand from founding agencies in the public, commercial, or not for profit sectors.

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. Executive Summary of EPOS 2020 Including Integrated Care Pathways. Rhinology. 2020;58(2):82–111. https://doi.org/10.4193/Rhin20.601.
2. Park IH, Lee JS, Park JH, et al. Comparison of the human microbiome in adults and children with chronic rhinosinusitis. PLoS ONE. 2020;15(12). https://doi.org/10.4193/Rhin20.601.
3. Anamika A, Chakravarti A, Kumar R. Atopy and Quality of Life in Pediatric Chronic Rhinosinusitis. Am J Rhinol Allergy. 2019;33(5):586–90. https://doi.org/10.1177/1945892419854266.
4. Chandy Z, Ference E, Lee JT. Clinical Guidelines on Chronic Rhinosinusitis in Children. Curr Allergy Asthma Rep. 2019;19(2):14. https://doi.org/10.1007/s11882-019-0845-7.
5. Stapleton AL, Shaffer AD, Morris A, et al. The microbiome of pediatric patients with chronic rhinosinusitis. Int Forum Allergy Rhinol. 2021;11(1):31–39. https://doi.org/10.1002/alr.22597.
6. Drago L, Pignataro L, Torretta S. Microbiological Aspects of Acute and Chronic Pediatric Rhinosinusitis. J Clin Med. 2019;8(2):149. https://doi.org/10.3390/jcm8020149.
7. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(29):1-464. https://doi.org/10.4193/Rhin20.600.
8. Delemarre T, Holtappels G, De Ruyck N, et al. Type 2 inflammation in chronic rhinosinusitis without nasal polyps: Another relevant endotype. J Allergy Clin Immunol. 2020;146(2):337-343. https://doi.

org/10.1016/j.jaci.2020.04.040.

9. Belcher R, Virgin F. The Role of the Adenoids in Pediatric Chronic Rhinosinusitis. Med Sci. 2019;7(2):35. https://doi.org/10.3390/medsci7020035.
10. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: Pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–553. https://doi.org/10.1177/0194599814549302.
11. Neff L, Adil EA. What is the role of the adenoid in pediatric chronic rhinosinusitis? Laryngoscope. 2015;125(6):1282–1283. https://doi.org/10.1002/lary.25090.
12. Beswick DM, Messner AH, Hwang PH. Pediatric Chronic Rhinosinusitis Management in Rhinologists and Pediatric Otolaryngologists. Ann Otol Rhinol Laryngol. 2017;126(9):634–9. https://doi.org/10.1177/0003489417719717.
13. Heath J, Hartzell L, Putt C, et al. Chronic Rhinosinusitis in Children: Pathophysiology, Evaluation, and Medical Management. Curr Allergy Asthma Rep. 2018;18(7):37. https://doi.org/10.1007/s11882-018-0792-8.
14. Vasco CTC, de Morais HC, Avelino MAG. Systematic review of the literature on surgical treatment of chronic rhinosinusitis in children: What is the best approach? Rev Paul Pediatr. 2020;38. https://doi.org/10.1590/1984-0462/2020/38/2018068.
15. Bulfamante AM, Saibene AM, Felisati G, et al. Adenoidal Disease and Chronic Rhinosinusitis in Children-Is there a Link? J Clin Med. 2019;8(10):1528. https://doi.org/10.3390/jcm8101528.
16. Shinee T, Sutikno B, Abdullah B. The use of biologics in children with allergic rhinitis and chronic rhinosinusitis: Current updates. Pediatr Investig. 2019;3(3):165-172. https://doi.org/10.1002/ped4.12146.
17. Seresirikachorn K, Chetthanon T, Suwansirisuk T, et al. Low-dose macrolides for treating pediatric rhinosinusitis: A retrospective study and literature review. SAGE Open Med. 2020;8. https://doi.org/10.1177/2050312120933642.
18. Chong LY, Piromchai P, Sharp S, et al. Biologics for chronic rhinosinusitis. Cochrane Database Syst Rev. 2021;3(3). https://doi.org/10.1002/14651858.CD013513.
19. Smith KA, Pulsipher A, Gabrielsen DA, et al. Biologics in Chronic Rhinosinusitis: An Update and Thoughts for Future Directions. Am J Rhinol Allergy. 2018;32(5):412-423. https://doi.org/10.1177/1945892418787132.
20. Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019;74(12):2312-2319. https://doi.org/10.1111/all.13875.