

Medical algorithm: Diagnosis and treatment of chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is a disease affecting more than 10% of the European population, causing symptoms and impacting quality of life. CRS is classically differentiated into disease without and with nasal polyps (CRSsNP, CRSwNP) based on clinical signs, specifically using nasal endoscopy for diagnosis.¹ However, the differentiation into phenotypes allows to conclude on dominant remodelling patterns (fibrosis in CRSsNP or oedema and polyp formation in CRSwNP), but does only partly predict the natural course of disease; phenotypes do not adequately appreciate the current discussion about different surgical approaches or innovative biologics. Therefore, endotypes have recently been introduced to reflect relevant pathomechanisms with impact on the diagnosis, prognosis and finally treatment.² (Table 1)

In short:

- CRSsNP mostly is characterized by non-type 2 inflammatory disease, may express IL-17 or related cytokines in some patients, and has low asthma comorbidity.
- A third of the subjects with CRSsNP also expresses mild type 2 inflammation, mostly related to allergic airway disease, with increased early-onset asthma comorbidity.
- CRSwNP should be differentiated into type 2 (typically involving cytokines IL-4, IL-5 and IL-13, eosinophils and IgE) and non-type 2 inflammatory diseases (may involve IL-17, neutrophils).
- The majority of CRSwNP in Europe is characterized by moderate type 2 inflammation, but also may be severely inflamed (with cytokine concentrations significantly higher than mild-moderate type 2 disease) and high late-onset asthma comorbidity (up to 70%).
- Type 2 currently can be defined based on the comorbidity of late-onset asthma, increased blood eosinophils (>150/mL, the higher the better) and an increased total serum IgE (>150 kU/L, the higher the better) showing polyclonality, or prior histopathological results.

Whereas there is type 2 CRSsNP, mostly with mild inflammation, and these patients have more early-onset asthma and respiratory allergies as comorbid disease than those with non-type 2, it has not been elaborated whether these patients have a different prognosis after intervention or should be treated differently in terms of pharmacotherapy or surgery.² Pharmacotherapy for all CRSsNP includes topical glucocorticosteroids, antibiotics for acute episodes and eventually long-term macrolides; surgery may be best described as “functional

endoscopic sinus surgery (FESS)” sparing sinus mucosa, but opening the sinus accesses; and no biologics have been tested in this population yet. Figure 1 describes the diagnostic and therapeutic management of CRSsNP and CRSwNP.

In CRSwNP, the expression of type 2 inflammation rather is moderate to severe, varies in percentage of concerned patients and degree of inflammation all over the world³ and is associated with the risk of late-onset asthma comorbidity, multimorbidity and recurrence of disease after surgery.^{4,5} Moderate-severe CRSwNP not responding to topical glucocorticosteroids (GCS), doxycycline long-term and short courses of oral GCS represents the most difficult to treat CRS population, possibly associated with late-onset, often nonatopic moderate to severe type 2 asthma and the need for repeated surgery in lifetime (average 3–4, possibly more than 10 surgeries). This patient group shows the highest unmet need, but may profit from more extended “reboot surgery”⁶ and the future use of biologics.^{7,8}

Surgery in CRSsNP is generally thankful, with a high likelihood of success in patients correctly diagnosed (based on a history of typical symptoms longer than 6 months and a CT scan showing clear signs of CRS after adequate medical treatment), and surgery performed according to the ideas of Messerklinger/Stammberger as mucosa-sparing approach.¹ In contrast, surgery according to the same aforementioned principles may work in non-type 2 CRSwNP, but will often fail in moderate and in the majority of patients with severe type 2 inflammation.⁹ Therefore, sinus surgery more often is performed in an “extended approach,” widely opening the sinus ostia to allow postoperative local GCS treatment, also involving the frontal sinuses (“Draf 3” operations). Recent data however recommend the total removal of the inflamed sinus mucosa (Reboot surgery⁶), maintaining the nonpolyp forming nasal mucosa, which then overgrows the sinuses to cover the sinus bones within 8 weeks. The results of a first retrospective study indicate a significantly lower recurrence rate⁶ over 3 years. However, this principle is not generally accepted yet, and certainly can only be performed by experienced surgeons. In general, long-term results published for surgery are scarce, are mostly published by highly specialized tertiary care institutions and therefore cannot be assumed to be representative for every form of “sinus surgery.”

Starting in 2006 with a first publication of innovative biologics in CRSwNP, three further proof-of-concept studies have been performed^{7,8} and paved the way for just finished or currently ongoing Phase 3 studies with dupilumab, omalizumab, mepolizumab and benralizumab. These monoclonal antibodies target the typical type

Phenotype	Endotype	Asthma comorbidity	Recurrence risk (estimated from limited data and clinical experience)
CRSsNP	Non-type 2	App. 10%, early onset	Very low
	Type 2	<40%, early onset	Low
CRSwNP	Non-type 2	10%	Low
	Type 2 (moderate)	<40%, late-onset	Moderate
	Type 2 (severe)	Up to 70%, late-onset	High

TABLE 1 Pheno- and endotypes of CRS and clinical consequences

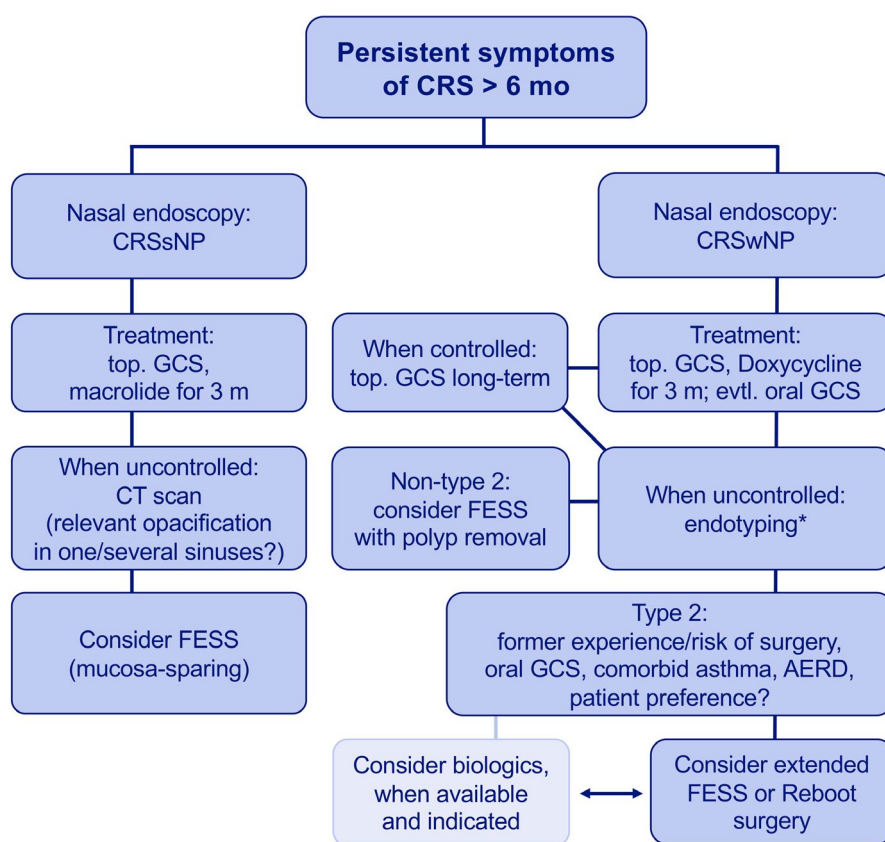


FIGURE 1 Management algorithm for chronic rhinosinusitis (CRS, suggestion of the authors). *Type 2 markers: late-onset asthma, increased blood eosinophils, elevated total IgE, polysensitization and others [Color figure can be viewed at wileyonlinelibrary.com]

2 cytokines IL-4 and IL-13 via blocking the IL-4 receptor alpha (dupilumab), IL-5 (mepolizumab) and IL-5 receptor alpha (benralizumab), as well as IgE (omalizumab); further antibodies are considered. The proof-of-concept studies mentioned⁷ indicated that all the targets could be beneficial in reducing nasal polyp mass (nasal polyp score) and safe in severe CRSwNP patients, but showed differences in their efficacy on quality of life parameters, smell, comorbid asthma and sinus involvement, and specifically demonstrated different responder rates. However, for a reasonable comparison between those biologics, the results of the Phase 3 studies should be awaited. The presentation of the first Phase 3 dupilumab studies at the recent AAAAI meeting indicated that the drug, added to a standard-of-care corticosteroid nasal spray, significantly reduced nasal polyp size,

nasal congestion severity, and the need for systemic corticosteroids and/or surgery over a 24 weeks study period vs. placebo in patients with bilateral nasal polyps who, despite treatment with systemic corticosteroids in the previous 2 years or history of surgery, continued to have ongoing moderate or severe symptoms of nasal congestion, blockage, loss of smell or nasal discharge. In a group of patients with comorbid asthma or AERD (app. 59% and 28% of subjects), dupilumab also significantly improved lung function and asthma control. The rates of adverse events were generally similar across dupilumab and placebo, and no new or unexpected side effects were observed.

Appreciating current practice and these new developments, a innovative algorithm for diagnosis and treatment of different pheno- and endotypes of CRS has been developed, which needs step-wise

confirmation. With the rapidly increasing knowledge in this area, including the search for suitable biomarkers, the algorithms also will need adjustment in due time. The current developments will impact the current management of CRS.

CONFLICTS OF INTEREST

CB is advising and speaker for Sanofi, GSK, Novartis and Astra-Zeneca.

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REFERENCES

1. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012;23(3):1-298.
2. Tomassen P, Vandeplas G, van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol.* 2016;137(5):1449-1456.
3. Wang XD, Zhang N, Bo M, et al. Diversity of T-helper cytokine-profiles in chronic rhinosinusitis: a multicenter study in Europe, Asia and Oceania. *J Allergy Clin Immunol.* 2016;138(5):1344-1353.
4. Van Zele T, Holtappels G, Gevaert P, Bachert C. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy.* 2014;28:192-198.
5. Vlamincck S, Vauterin T, Hellings PW, et al. The importance of local eosinophilia in the surgical outcome of chronic rhino-sinusitis: a 3-year prospective observational study. *Am J Rhinol Allergy.* 2014;28:260-264.
6. Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic sinus surgery for type-2 CRSwNP: an endotype-based retrospective study. *Laryngoscope.* 2019. <https://doi.org/10.1002/lary.27815>
7. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. *J Allergy Clin Immunol.* 2015;136(6):1431-1440.
8. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA.* 2016;315(5):469-479.
9. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope.* 2017;127:550-555.