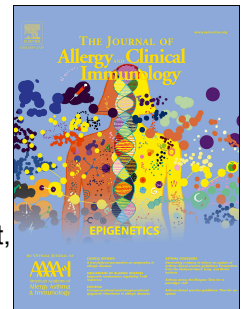


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Rostrum

Endotypes of chronic rhinosinusitis: impact on management

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Short abstract

Following the trend in asthma, endotypes for chronic rhinosinusitis with nasal polyps (CRSwNP) have been established, with Type 2 immune reactions representing 80-100% of nasal polyp cases in Europe and the US. Endotyping is without doubt useful to predict the natural course of disease, to determine pharmacotherapy and the extent of surgery, and lately also to select patients for Type 2 biologics. However, with the opening of this new era of treatment, also limitations of the current possibilities in subgrouping patients became apparent, as 1) mixed endotypes often can be found and 2) predictions on the best biologic to be used in an individual patient are not possible yet. Some of the questions to address in the near future are discussed.

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Keywords: chronic rhinosinusitis, nasal polyps, endotypes, type-2 inflammation, surgery, biologics

Conflict of interest

C. B. acted as speaker and member of advisory boards for Sanofi-Aventis, Novartis, Glaxo, Astra-Zeneca, Stallergenes, ALK, Asit Biotech, Mylan, Allakos.

Endotyping of Chronic Rhinosinusitis is a recent development, which we here shortly summarize. In 2013, a PRACTALL document was elaborated in a co-operation between the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology and published in the Journal of Allergy and Clinical Immunology (1). The document described the limitations in the knowledge on pathomechanisms as a major obstacle in understanding the causes of chronic rhinosinusitis (CRS) and in improving its treatment. Although clinically relevant CRS phenotypes have been defined by observable characteristics and treatable traits, such as the presence or absence of nasal polyps, it was clear that phenotypes may be based on different underlying pathomechanisms, which may provide an innovative and relevant differentiation of disease subgroups: endotypes based on biomechanistic principles. At that time, several smaller proof-of-concept studies were already published, using innovative treatments or “biologics” in CRS with nasal polyps (CRSwNP), including Reslizumab, Mepolizumab and Omalizumab (2, 3, 4), and other studies with monoclonal antibodies were to be performed. These studies, all initiated at Ghent University, made use of the fact that in Belgium more than 80% of nasal polyps show a Type 2 signature and thus may respond to the treatment (see ref 21).

Another source for the development of endotypes was the natural course of the disease is the involvement of the lower airways, mostly described as asthma co-morbidity. This involvement is typically late-onset and increases with the severity of inflammation. Endotypes of asthma have been described recently, providing new insights into key pathogenic mechanisms for a complex, heterogeneous disease (5). Also asthma often is characterized by Type 2 inflammation; the Type 2 high endotype can have either an allergic or non-allergic background and is typically characterized by some degree of eosinophilic airway inflammation (6). Aspirin-exacerbated respiratory disease (AERD) has also long been recognized as a unique asthma phenotype carrying a Type 2 signature. Increased exhaled nitric oxide (FeNO) and blood eosinophil counts are biomarkers for type 2 endotype bronchial asthma, specifically useful in the identification of severe asthma with frequent exacerbations, about a third of the asthma population (7). Other co-morbidities may further characterize Type 2 airway disease (8). Thus, endotyping of CRS helps to understand and predict the natural course of disease and to choose the adequate treatment from pharmacotherapy to surgery and biologics. Figure 1 summarizes strong and possible indicators for Type 2 immune reactions in CRS. As indicated in Figure 1, we do not necessarily need blood or serum biomarkers for the identification of a Type 2 immune response; the presence of late-onset asthma, and even more of non-steroidal anti-inflammatory drug (NSAIDs)-exacerbated respiratory disease (N-ERD) with the asthma, increases the likelihood of a Type 2 endotype to near to 100 %. It was thus the right time point to introduce the concept into clinics for the upper airways also, and develop biomarkers and individualized care pathways for CRS based on a differentiation into Type 2 and non-Type 2 endotypes. In the last 5 years, more than 60 publications have been written on chronic rhinosinusitis with the term endotype in the title.

The first analysis of CRS endotypes, primarily based on measurements of cytokines and mediators in the sinus mucosa and secondarily related to clinical traits, was published in 2016 (9). This analysis showed that asthma comorbidity and recurrence of disease after surgery were both associated with

increased mucosal concentrations of interleukin(IL)-5, ECP, IgE and *Staphylococcus aureus* enterotoxin-specific (SE)-IgE, undoubtedly reflecting Type 2 inflammation. The Chicago group added to these findings that smell loss and “allergic mucin” was significantly associated with the presence of the Type 2 endotype (10); whereas loss of smell is a frequent sign of severe polyposis, allergic mucins only affects a small population.

Type 2 inflammation is characterized by the activation of T helper 2 cells and innate lymphocyte cells (ILC2) (11, 12, 13), producing the key cytokines IL-4, IL-5, and IL-13. Epithelial cells triggered by *Staphylococcus aureus* and releasing IL-33 may initiate the flow of events (14, 15). It is necessary to mention that “Type 2” often is not as “pure” as often thought. The typical sticky “allergic mucin” most likely is caused by the release of eosinophil extracellular traps (EET) containing DNA and major basic protein (MBP), but also galectin-10, resulting in the deposition of Charcot-Leyden crystals (CLCs) (16, 17). These CLCs, however, induce a strong neutrophilic invasion on their own, adding to the inflammatory load of the mucosa (18). In less severe inflammation, interferon-gamma and interleukin-17 may also induce neutrophilic inflammation side to side with the presence of eosinophil granulocytes (19, 20). However, the fact that more than 80% of bilateral nasal polyps – and thus the vast majority - are “Type 2” with or without comorbid Type 1/3 inflammation (9) led to the fact that non-Type 2 nasal polyps were neglected in the strategy for biologic treatment. Furthermore, the identification of useful biomarkers for endotyping of CRS in daily practice seems difficult, as blood eosinophils and serum IgE are often normal in Type 2 nasal polyps without asthma, and the principle of endotyping based on Type 2 inflammatory cytokines in nasal secretions or tissue biopsies is laborious to introduce. Importantly, although Type 2 inflammation characterizes the majority of nasal polyp patients, and obviously leads to more severe clinical expression of disease, it may not be neglected that other non-Type 2 mechanisms also play a role, and may be very relevant in specific situations to be discussed later.

Phenotypes vs. endotypes: Decisive for treatment optimization concerning surgery and biologics

For a clinician, the symptoms of CRS include nasal obstruction, nasal secretions, post-nasal drip, loss of smell, and headache or pain/pressure over the sinuses. Typically, CRSsNP patients have more pain, and CRSwNP patients rather suffer from loss of smell. The CT scan shows opacification of one or several sinuses, and an experienced physician may already be able to make differential-diagnostic considerations, also including fungal disease, cystic fibrosis and others. However, nasal endoscopy actually delivers the main criterion to differentiate between CRSsNP and CRSwNP: bilaterally visible nasal polyps clearly point to the diagnosis of CRSwNP, the etiology of which still has to be clarified, but the lack of visible polyps does not totally exclude the disease. In fact, nasal polyps are derived from the sinuses, as the nasal mucosa does normally show less ability to form polyps, the expression of “nasal polyps” therefore is misleading. So far, nasal polyps have been treated alike all over the world, with some local flavour to the surgery performed and often not different from surgery for CRSsNP. And physicians have been more or less successful with their surgery, as polyps may be non-Type 2 and do not recur, or they are Type 2 and tend to recur with increasing impact of the inflammation (9). Studies have clearly indicated variations of the Type 2 – Non-Type 2 distribution all over the world, with Type 2 dominating CRSwNP in Europe, the US and Australia, but less in China and other Asian countries (21, 22, 23).

Thus, the surgical approach to CRSwNP obviously needs to be adapted and differentiated worldwide, depending on the endotype and the degree of inflammation, and the approach needs to be different

from that in CRSsNP (12). Avoidance of recurrence of disease is an important target, and consecutively the surgical technique needs to adjust to this target and thus to the disease endotype, in order not to over- or undertreat sinus disease. After focusing on mucociliary clearance and narrow clefts to explain CRS, the focus of surgery finally shifted to the mucosa and its inflammation. Specifically unresponsive to “conventional sinus surgery” was severe Type 2 CRSwNP disease, with recurrent polyps after a few months and persistent oedema and symptoms (24). To completely remove the sinus mucosa, including the polyps, but also the thickened and equally diseased mucosa next to them (Jonstam K et al, submitted) prepared to develop polyps also, may be a valid approach to a severe Type 2 mucosal disease involving all sinuses (25). This approach has been termed “reboot”, involving also the frontal sinuses and building up on the observation that the new mucosa growing into the sinuses from the nasal cavity shows less polyp formation. Nasal mucosa also may show Type 2 bias, but does very rarely form polyps, and thus overgrows the sinuses as a thin but functional mucosa within a few weeks after surgery. Whether this principle can be executed by many physicians, who obviously need to be highly skilled, and will be able to maintain the polyp-free condition for many years near to all patients, remains to be shown. Further, the idea of endotype-based approaches to surgery has only been taken up by a few physicians, and indicative studies still need to be performed. Currently, CRS with and without polyps is often treated following the same principles of “functional endoscopic sinus surgery”. Thus, we are undoubtedly at a turning point in the management of patients with severe CRSwNP, persisting after pharmacological treatment and even previous surgery, and endotyping is an important part in this development targeting mucosal disease (9).

The first biologic for the indication CRSwNP, Dupilumab, has just been registered in the US and Europe, and its wide-spread use in this indication will soon develop. As mentioned, this progress followed and built up on studies with Reslizumab, Mepolizumab and Omalizumab (2, 3, 4), recently completed by Dupilumab in phase 2 and 3 studies (26, 27). The last studies in this sequence, two Phase 3 parallel trials with Dupilumab vs. placebo over 24 and 52 weeks, impressively demonstrated the shift of borders for monoclonal antibodies in CRSwNP, with two thirds of the patients reacting with a clinically significant decrease in polyp mass and in symptoms, and an impressive fast onset of action specifically concerning sense of smell. Smell improved within the first two weeks already, faster than the polyp mass, and anosmia turned at least into hyposmia in about two thirds of the 76% of subjects over 24 weeks in those who were anosmic at start of study. This again clearly demonstrated the role of Type 2 inflammation in the induction of loss of smell, with an effect of the anti-IL-4/13 principle likely (Dupilumab) surpassing that of anti-IL5 (Mepolizumab) or anti-IgE (Omalizumab). Type 2 cytokines have been shown to be reduced in nasal secretions under Dupilumab therapy (28). The effects of biologics clearly confirm the role of Type 2 immune disease in the symptomatology related to CRSwNP in the majority of patients - but not all, specifically those non-responding to the drug. How can we understand non-responders when treating Type 2 CRSwNP with the anti-Type 2 drug par excellence? Is it possible that Type 2 is not one entity, and subgroups exist within Type 2 CRSwNP? Although some patients just may need more time to react to the treatment with a decrease in nasal polyp score, or may need higher dosage at least at the start of treatment to overcome the strong inflammation, those patients who only marginally or not at all respond to the treatment raise questions. Is it a question of dosing only, or do we need to appreciate the impact of different endotypes in a Type 2 immune response at first sight, and thus combine different treatments to reach our goal in those patients?

New questions to address

Although Type 2 inflammation regularly dominates the scene in “eosinophilic” nasal polyps, neutrophils may be present also, either driven by IL-17 or by CLCs, as specified above. The relevance of this neutrophilic inflammatory part is unclear so far: will it just disappear with the biologic treatment directed towards Type 2, specifically if it is induced by CLCs, or will it persist or even expand, driven by IL-17, once the Type 2 reaction is suppressed? Is Type 1 or Type 3 inflammation causing failure in dominant Type 2 inflammation, and associated with non-response? Is only the purely non-Type 2 neutrophilic polyp not responding to biologic treatment? Or is lack of response also seen in eosinophilic nasal polyps with specifically severe inflammatory signatures? Are there different reactions in different patients and conditions? And finally, do we need to apply different targeted therapies in parallel to overcome the problem in some patients? Would it be advantageous to combine strategies directed towards IL-5 and IL-4/13, at least at start of treatment, to obtain a faster, better and broader response? Thus, with the complete understanding of endotyping in CRSwNP still remaining a challenge, can we already make the step to translation into daily practice? This dilemma is provoking a lot of questions to be answered; in simple words, a tissue eosinophil – or even less a blood eosinophil – does not make a Type 2 diagnosis with clear therapeutic consequences yet. Only large clinical trials with biologics including solid research into mucosal tissue, nasal secretion and blood biomarkers will finally enable us to answer the above listed questions.

Whereas for Type 2 asthma, a preference concerning the antibody approach to be selected has been provided (29), focusing on the allergic aspect of severe asthma primarily, and on blood eosinophils in severe asthmatics thereafter, no such preference and care pathways have been elaborated for CRSwNP. The reason is that no parameter which would be associated with treatment response, neither in the blood, serum, nor nasal secretions or tissues has been identified for any biologic yet. Severe CRSwNP patients do show elevated levels of serum IgE and blood eosinophils, and may be allergic to inhalant allergens or not, and only then there is rationale to apply any of the mentioned Type 2 biologics; however, there are still no markers to predict response of an individual patient to any of the biologics, which could be derived from the current studies. Thus, how do we decide on the order of the biologic to try first? In a situation, where only one biologic, Dupilumab, is available for the indication CRSwNP, the question is easy to answer. However, we will likely have four or more biologics within a year or two, and as for asthma, arguments may be pushed forward to direct the choice based on eosinophils, allergy or IgE. For the sake of patients and the community, arguments should rather focus on efficacy, responder rates, safety, and possibly costs of treatment.

Lacking biomarkers to predict the right drug for an individual Type 2 CRSwNP patient, the approach to “treat with the first choice and observe the response” seems the best we can do at the moment; however, in all studies performed with biologics so far, a third to nearly half of the patients did not respond sufficiently to the treatment, and evidence-based stopping rules have to be introduced in due time to identify non-responders early after start of treatment as a compromise. Fortunately, different from severe asthma, in which exacerbations at longer time periods need to be observed and counted, the follow-up in CRSwNPs will be easier. First, there is the smell, which may come back within 4-8 weeks (27, 30), and may serve as a very strong sign of response to treatment; the patient will be very pleased to report this phenomenon to the physician! However, in patients with repeated surgeries and older life time, smell cannot be regained and therefore cannot serve as a criterion. Second, nasal endoscopy is relatively easy to perform and standard among ENTs, and even if the nasal polyp score is not familiar to all colleagues, a screenshot of the nasal endoscopy can be taken easily before treatment start and compared to the situation 3 to 6 months later. And, although many of us do not use visual analogue scales (VAS) or SNOT-22 on a regular basis in daily practice, the

patient will happily report the changes observed. Smell testing and nasal polyp scoring easily delivers the objective measures to confirm treatment response. The nose really is easy to access for control.

Conclusions

For CRSwNP, endotyping thus makes a great difference in our clinical practice and provides the basis for progress in understanding and treating our patients better. At the same time, surgical techniques and skills and our understanding of immunology “in practice” need to be improved. Whereas clinical signs of CRS with or without polyps and its comorbidities allow to phenotype the patients with sinus disease, they also may be indicative for the endotypes of CRS; this allows us to predict the natural course of disease and to select adequate treatment approaches – with increasing importance - from pharmacotherapy to surgery and finally to biologic agents (Figure 2). It needs no discussion that the indication of a biologic drug such as Dupilumab, Omalizumab, Benralizumab or Mepolizumab should be strictly based on Type 2 indicators, for any individual patient (30). These indicators will need continuous adjustment based on large databases to improve the selection of patients specifically for biologics, but also for adjusted surgical approaches. Endotyping in CRS will accompany us for long time, will be the motor for progress in diagnosis and treatment, and likely will increase the demand for specialised centres. May be this is the way for the specialists of the upper and lower airways to work together even closer.

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Figure Legend

Figure 1: **How to identify Type 2 CRSwNP:**

Figure 2: **Impact of Type 2 endotype on CRS treatment**

How to identify Type 2 CRSwNP

Likelihood of Type 2 CRSwNP*

1) Clinical traits

• Bilateral CRSwNP without comorbidity	> 80%
• Allergic sensitization	> 90%
• One or more effective oral GCS courses in last year	> 90%
• Comorbid late-onset asthma	> 90%
• N(SAID)-ERD	100%
• Former surgery with tissue eosinophilia (histology)	100%

2) Biomarkers

Blood eosinophils > 150/µl	> 90%
Serum IgE high, polyclonality	> 90%
Serum SE-IgE positivity	100%

* data from the Upper Airways Research Laboratory data base, C. Bachert, Ghent University

	Preferred Pharmacotherapy	Preferred Surgery	Preferred Biologics
Non-Type 2	Macrolide antibiotics	Conventional FESS	None currently in registration
Type 2	• Topical GCS, oral GCS • Doxycycline	Extended surgery/ Reboot surgery	• Type 2 biologics (Dupilumab) • Eventually other Type 2 biologics • Depending on indication for CRSwNP

Uncontrolled severe CRSwNP: Decision on surgery vs./in combination with biologics should be made with the patient, based on former management and effects thereof, as well as efficacy and side effects/complications of biologics and surgical approaches