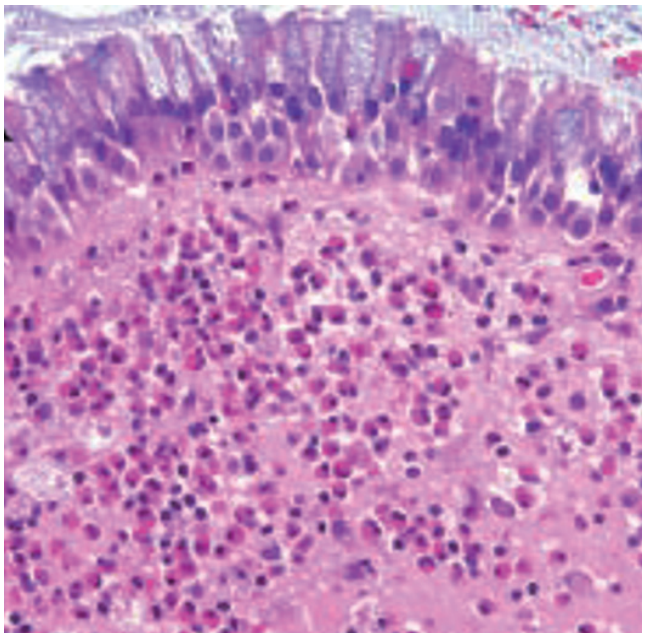
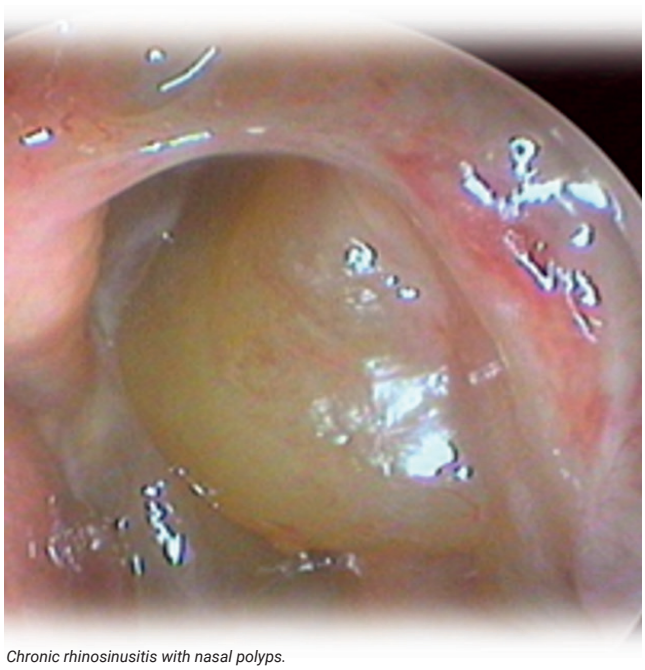
Endotypes in chronic rhinosinusitis: clinical relevance

BY J PABLO STOLOVITZKY

Identifying endotypes enables personalised therapies that target specific pathophysiological processes, potentially resulting in better treatment outcomes for patients.



Ten or more eosinophils per high power field.



Chronic rhinosinusitis with nasal polyps.

The contemporary model of chronic rhinosinusitis (CRS) pathogenesis revolving around endotype, in combination with an expanding toolbox of diagnostics and therapeutics, enables clinical rhinologists to offer a personalised approach to the management of this complex disease.

CRS is defined as the presence of ≥2 of the four cardinal symptoms for ≥12 weeks: nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) must be present, with or without facial pain/pressure or a reduction/loss in the sense of smell [1,2].

CRS, a syndrome with multifactorial aetiology, arises from dysfunctional interactions between environmental factors and the host immune system. The endotype's intensity and nature significantly influence the observed phenotype. The immune response then triggers tissue remodelling that forms the basis of the familiar phenotypic presentations we see in the clinic, including polyp formation, fibrin deposition, acanthosis, and desquamation. Advances in rhinologic translational research enabled the application of these concepts to contemporary clinical practice.

Endotype identification

Endotype dominance is divided into type 2 and non-type 2, which are based on the inflammatory mechanisms at work. Large extracellular parasites are the target of type 2 responses, which include an initial response from innate lymphocyte subset two, which produces interleukin 4, 5, and 13 quickly, and an adaptive immunity-based response from Th2 cells, which creates a more specialised, delayed response [1].

Type 1 and type 3 endotypes are collectively referred to as non-type 2. Type 1 responses involve innate and delayed immunity by Th1 lymphocytes producing the cytokine interferon-γ and directing their defences toward intracellular invaders, most often viruses. Type 3 responses target extracellular bacteria and fungi and result in an innate and delayed production of interleukin 17 and 22 [1].

In clinical practice, we are not yet able to evaluate the above-mentioned biomarkers. While there isn't complete agreement to define type 2 endotype, EPOS 2020 suggests a threshold of 10 or more eosinophils/HPF, blood eosinophils ≥250/μL and serum IgE levels ≥100UI/mL

There is not complete agreement on the threshold to define type 2 endotype but EPOS2020 supports 10 or >/HPF [1,4]. Similarly, ≥250 blood eosinophils/μL and serum IgE levels ≥100 UI/mL are indicative of the type 2 endotype.

CRS classification by endotype dominance

While CRS has historically been clinically classified based on phenotype, the 2020 European position paper on rhinosinusitis and nasal polyps [1] and Grayson et al [3] classified primary and secondary CRS according to (i) anatomic distribution, (ii) endotype dominance, and (iii) phenotype examples. Anatomic distribution is divided into localised (unilateral) or diffuse (bilateral) disease. The new classification system also forms the basis of comprehensive care pathways, with endotype identification

> "The new classification system also forms the basis of comprehensive care pathways, with endotype identification playing a key role in the diagnostic decision tree"

playing a key role in the diagnostic decision tree.

Non-type 2 endotype patients most often present with nasal discharge and facial pain, whereas patients with type 2 endotype usually complain of smell loss or nasal blockage/congestion. Most patients are not aware of their olfactory impairment, and smell tests such as the North American UPSIT or European ODOFIN Sniffin' Sticks can objectively evaluate a patient's olfactory status.

Patients with non-type 2 endotype usually have less asthma and atopy, while type 2 endotype patients often exhibit asthma and/or NSAID-exacerbated respiratory disease and a positive skin prick test or serum IgE levels ≥100 UI/mL. On nasal endoscopy, non-type 2 endotype patients present with purulence, whereas type 2 endotype patients show polyps and eosinophilic mucin.

Endotype-driven treatment regimens in primary diffuse CRS

Let us walk through some examples of practical endotype identification in primary, diffuse CRS after six to 12 weeks of appropriate medical therapy (AMT) without improvement, and the subsequent endotype-driven treatment options.

Therapeutic choices include AMT in combination with pharmacological therapy and/or functional endoscopic sinus surgery (FESS). After endotype identification, AMT may be combined with long-term antibiotics (>4 weeks) for their immunomodulatory properties. Clarithromycin should be considered for non-type 2 endotype patients as it targets neutrophilic inflammation. For type 2 endotype patients, oral corticosteroids should be considered along with Doxycycline which suppresses IgE and decreases polyp size by inhibiting the matrix metalloproteinases involved in tissue remodelling [5].

In the case of surgery, minimally invasive sinus surgery to create a sinus cavity that incorporates the natural ostium is considered sufficient for non-type 2 endotype patients. This will allow adequate sinus ventilation, facilitate mucociliary clearance, and facilitate the application of topical therapies. Full FESS, including large middle meatal antrostomies, total sphenoid-ethmoidectomy, and extended frontal sinusotomy (such as Draf IIb or III), is preferred for type 2 endotype patients.

Phenotypes associated with the endotypes of primary diffuse CRS

Non-type 2 endotype manifests itself as non-eosinophilic CRS. Phenotypic examples of the type 2 endotype include eosinophilic CRS, CRS with nasal polyps, allergic fungal rhinosinusitis, and central compartment allergic disease [1,3].

Biological treatment of CRS with nasal polyps (CRSwNP)

The criteria that indicate the use of biologics in the treatment of CRSwNP overlap with the characteristics of type 2 CRS. Biologics are usually considered for patients with bilateral polyps and who have had endoscopic sinus surgery, although the trend is that clinicians are more frequently indicating biologics for patients with CRSwNP who have not undergone surgery. The qualifying criteria include evidence of type 2 inflammation, significant loss of smell, and comorbid asthma – all characteristics of the type 2 endotype. The need for systemic corticosteroids and significantly impaired quality of life, as defined by a SNOT-22 score ≥40, round out the list of five criteria; three of which must be present to indicate the use of biologics [1].

In conclusion, endotyping facilitates diagnosis and the selection of the optimal treatment pathways for the CRS patient. Current clinical practice utilises serum IgE levels, blood eosinophil counts, and eosinophils per high-powered field in histopathology specimens as biomarkers for endotype dominance. Additionally, skin allergy testing and olfactory function tests offer complementary information. Endotyping enables the selection of pharmacological therapeutics targeting the inflammatory mechanism at work and guides us in the selection of endoscopic sinus surgery to achieve better results. Tailoring clinical decisions to the patient's endotype, rather than relying solely on phenotype, enables individualised treatment. This approach results in improved outcomes and greater patient satisfaction. Endotyping holds the potential to revolutionise CRS management by enabling personalised treatments, predicting outcomes, and fostering innovation in the field.

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology* 2020;**58(Suppl S29)**:1-464.
2. Orlandi RR, Kingdom TT, Smith, TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol* 2021;**11(3)**:213-739.
3. Grayson JW, Hopkins C, Mori E, et al. Contemporary classification of chronic rhinosinusitis beyond polyps vs no polyps: A review. *JAMA Otolaryngol Head Neck Surg* 2020;**146(9)**:831-8.
4. Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol* 2012;**2(5)**:376-85.
5. Pinto Bezerra Soter AC, Bezerra TF, Pezato R, et al. Prospective open-label evaluation of long-term low-dose doxycycline for difficult-to-treat chronic rhinosinusitis with nasal polyps. *Rhinology* 2017;**55(2)**:175–80.

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Declaration of competing interests:
None declared.