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EAACI POSITION PAPER

EUFOREA/EPOS2020 statement on the clinical considerations for CRSwNP care

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Abstract

Following the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) treatment algorithm for chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), patients suffering from severe uncontrolled CRSwNP are recommended to receive oral corticosteroids, (revision) sinus surgery, systemic biologicals and/or aspirin treatment after desensitization (ATAD). Given the major differences in indications, outcomes, practical considerations, risks and costs of these key pillars of treatment, there is a growing need to define criteria for each treatment option and list the clinically relevant and major considerations for them. This EUFOREA document therefore provides an expert panel overview of the expected outcomes, specific considerations and (contra)indications of the five major treatment arms of severe uncontrolled CRSwNP: oral corticosteroids, primary and revision sinus surgery, biological treatment and ATAD. This overview of treatment considerations is needed to allow physicians and patients to consider the different options in the context of providing optimal and personalized care for severe uncontrolled CRSwNP. In conclusion, the five major treatment options for severe uncontrolled CRSwNP have intrinsic advantages, specific indications and considerations that are of importance to the patient,

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ARS, American Rhinologic Society; ATAD, aspirin treatment after desensitization; CRSwNP, chronic rhinosinusitis with nasal polyps; CS, corticosteroids; EGPA, eosinophilic granulomatosis with polyangiitis; EPOS, European position paper on rhinosinusitis and nasal polyps; ERS, European Rhinologic Society; ESS, endoscopic sinus surgery; EUFOREA, European Forum for Research and Education in Allergy and Airway Diseases; INCS, intranasal corticosteroids; NCS, nasal congestion score; N-ERD, non-steroidal anti-inflammatory-exacerbated respiratory disease; NPS, nasal polyp score; NSAIDs, non-steroidal anti-inflammatory drugs; PROM, patient reported outcome measure; QoL, quality of life; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test-22; VAS, visual analogue scale.

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the physician and the society. This EUFOREA statement supports the unmet need to define criteria for the indication of every treatment pillar of CRSwNP.

KEYWORDS
aspirin intolerance, biologics, corticosteroids, CRSwNP, sinus surgery

1 | INTRODUCTION

The treatment for patients suffering from uncontrolled severe CRSwNP has been subject to a revolution of care given the growing insight into the underlying pathophysiology over the past two decades, the recommendation to evaluate biomarkers in the context of biologics and the increased awareness of comorbidities.[1–3] Chronic rhinosinusitis with nasal polyps (CRSwNP) is present in 1%–2% of the population. The terminology 'CRSwNP' is referring to a phenotype, and based on the increased understanding of underlying pathophysiology, we now rather refer to the term diffuse bilateral CRS.[1] Diffuse bilateral CRS can have a type 2 or non-type 2 endotype and present with or without polyps. In the western world, most of the diffuse bilateral CRS with polyps is of the type 2 endotype. However, in Asia, still a significant, although diminishing percentage of patients present with a non-type 2 endotype.[4,5]

A better understanding of the underlying inflammatory pathways has led to biologics emerging as an effective novel treatment option in the subtype of patients with type 2 disease. This option supplements the classic advanced treatment options after appropriate medical treatment with intranasal corticosteroid sprays or rinses for CRSwNP, such as oral corticosteroids and endoscopic sinus surgery.[6,7]

The European Forum for Research and Education in Allergy and Airway Diseases, EUFOREA, is an international not-for-profit organization aiming to prevent and reduce the burden of chronic respiratory diseases via the implementation of optimal care. In the context of CRS, a simplified treatment algorithm was launched, with the aim to educate all healthcare providers dealing with CRS on the treatment options and referral patterns, and to shorten the disease journey for CRS.[8] EPOS2020 is the 2020 version of the European Position Paper on Chronic Rhinosinusitis and Nasal Polyps. The expert teams of both organizations closely work together to improve management of CRS. Besides baseline treatment with nasal rinses and intranasal corticosteroids, the following five key pillars of specialist care have been used for uncontrolled severe CRSwNP based on personal history and disease journey: oral corticosteroids, primary and revision sinus surgery, biologics and aspirin therapy after desensitization (ATAD).

For several years, biologics have been indicated and are available in a growing number of countries for severe uncontrolled CRSwNP with the need to define specific criteria for the indication. In that context, EUFOREA has defined criteria for the indications of biologics in 2019,[9,10] which have been finetuned in 2023.[11] In contrast to biologics, no international consensus has been reached on the specific academic criteria for the indications of systemic corticosteroids, primary or revision sinus surgery or ATAD. Here, the EUFOREA/EPOS2020 expert panel of CRS supplemented with experts of the European Rhinology Society (ERS) and American Rhinology Society (ARS) have joined forces to agree on criteria, outcomes, contraindications and considerations in relation to the different treatment options for CRSwNP. The statements of the authors are based on extensive clinical experience and expertise and the current scientific knowledge in relation to each therapeutic option for CRSwNP.

2 | SYSTEMIC CORTICOSTEROIDS

The use of short courses of systemic corticosteroids (SCS) is an important tool in the treatment of severe CRSwNP due to their potent anti-inflammatory effects (see Figure 1).[1,12] SCS modulate the immune response with suppression of inflammation. These agents reduce the infiltration of inflammatory cells, inhibit the release of pro-inflammatory mediators and attenuate the vasodilation and oedema associated with CRSwNP.[1,12] The downregulation of inflammatory mediators results in reducing nasal polyp size and improving nasal congestion, smell dysfunction and other sinonasal symptoms.[12–14]

Systemic corticosteroids are an inexpensive and a globally available treatment, with effective reduction of nasal polyp size and rapid improvement of major sinonasal symptoms such as nasal obstruction, loss of smell and nasal discharge in both short- and long-term treatment.[12] SCS are often used in the management of acute exacerbations or as a short-term burst therapy because they can quickly reduce nasal polyp size and alleviate sinonasal symptoms, but evidence, including the optimal dose, is lacking. They are also commonly used for the management of asthma exacerbations in acute care settings, where usually doses of 1 mg/kg prednisolone equivalent to a maximum of 50 mg for 2–7 days are advised.[15–17] Comorbid patients with severe asthma (SA) and CRSwNP usually receive SCS more frequently as they work on both upper and lower airway symptoms, but local (intranasal and inhaled) long-term CS should be preferred.

Unfortunately, the effects of SCS wane shortly after ending treatment.[18] In view of significant systemic side effects observed with repeated short- or long-term courses such as osteoporosis, glaucoma, diabetes, cataract, hypertension, anxiety, insomnia, agitation, risk of adrenal suppression, increased appetite and reflux,[13,19,20] they are not recommended for maintenance treatment.[12] The EPOS 2020 criteria advise not to prescribe more than two courses of SCS per year because of the cumulative side-effects,[1] and Price et al.[19] comparing large groups of asthma patients with and without SCS use even showed a dose–response relationship for cumulative SCS exposure with most adverse

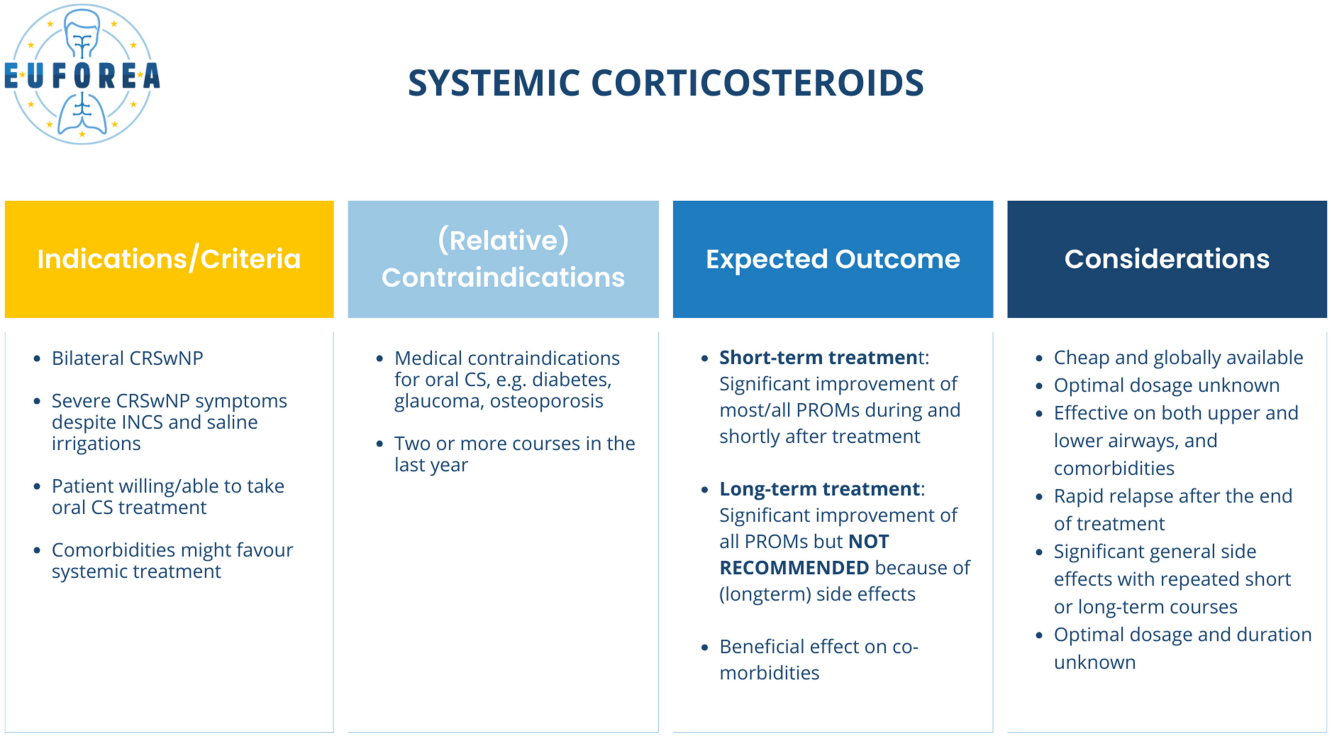

FIGURE 1 The indications/criteria, (relative) contraindications, expected outcomes and considerations when using systemic corticosteroids in the management of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP).

outcomes to begin began at cumulative exposures of 1.0 to <2.5 g and for some outcomes like e.g. diabetes mellitus and hypertension already at a cumulative exposures of only 0.5 to <1 g, equivalent to four lifetime SCS courses. Moreover, the willingness of the patient to use SCS should be considered, as some patients might fear the adverse effects.[21] The use of SCS should be considered extra carefully and weighed against the induced risks in patients suffering from certain conditions such as diabetes, glaucoma or osteoporosis.[12,22] In routine clinical practice, there is a significant heterogeneity in prescribing systemic steroids by clinicians in terms of type, dosage and treatment duration, partially explained by the lack of universally accepted modes of prescribing of systemic steroids over the years.[8,20,23,24]

3 | PRIMARY ENDOSCOPIC SINUS SURGERY

Primary ESS is indicated for severe unilateral or bilateral CRSwNP symptoms that persist or recur despite treatment with nasal rinsing, intranasal corticosteroids (INCS) and usually one or more courses of SCS within the preceding 2 years (see Figure 2).[1,25] Hence, the role of primary ESS managing CRSwNP is critical in cases where first-line medical therapy proves to be insufficient. Despite previous treatments, patients may report significant nasal obstruction as a consequence of large nasal polyps and nasal secretions filling the nasal cavities.

The primary goals of ESS in CRSwNP are to remove the diseased mucosa including nasal polyps, facilitate the delivery of intranasal corticosteroids to the sinuses, in turn reducing the inflammatory burden of the disease and improving the outcomes of post-EES medical treatment, with the expected outcome of improvement of overall sinonasal symptoms overall. ESS results in limited operative morbidity, rapid recovery (within weeks in most patients) and improved patient outcomes.[26] While both the expected outcome and the recurrence rates of ESS vary depending on factors such as the elapsed time since surgery, the extent of the procedure, the presence of comorbidities and the exposure to environmental/occupational irritants, most patients do well after sinus surgery.[27–29] Furthermore, ESS has shown effectiveness in reducing both upper and lower airway inflammation.[30–33] Although evidence is limited, the expert panel advises against performing a polypectomy without a complete ESS, although consensus is lacking about the extent of ESS and whether it should be based on the radiological extent of the disease or the endotype of CRSwNP.

Some patients might, however, fear general anaesthesia and/or ESS and think surgery is only a temporary solution.[34] In addition, while in the short-term significant improvements are observed both in upper and lower airway symptoms, regular saline rinsing and INCS use is needed to ensure good results both in the mid-term (one to 5 years post-surgery) and long-term (more than 5 years post-surgery).[31,35,36] ESS might also be contra-indicated in patients with medical/surgical contra-indications for anaesthesia and surgery, such as in patients with severe uncontrolled asthma. Physicians should also keep in mind that there can be considerable indirect cost related to ESS due to sick leave after the procedure.[37]

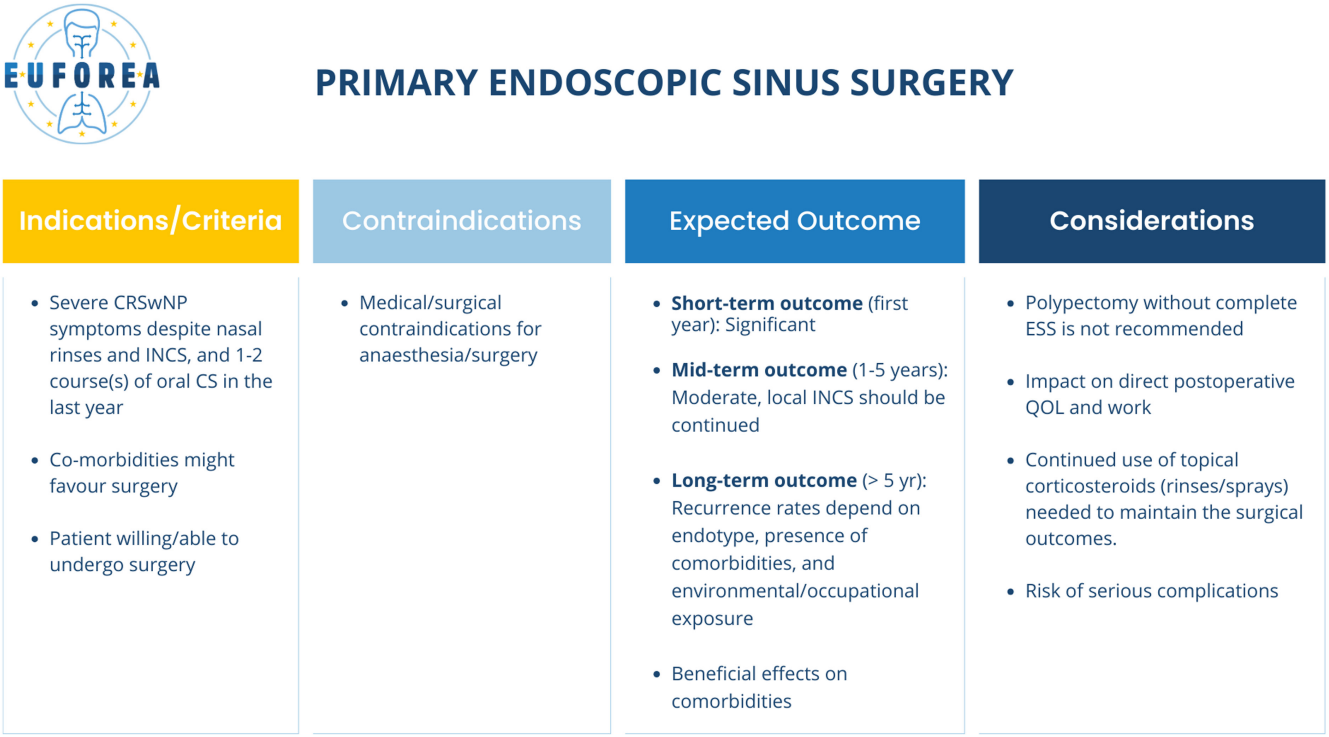

FIGURE 2 The indications/criteria, (relative) contraindications, expected outcomes and considerations when using primary endoscopic sinus surgery in the management of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP).

4 | REVISION ENDOSCOPIC SINUS SURGERY

Primary ESS provides effective relief and a good control of symptoms in the majority of the patients (see Figure 3).[27] However, several studies have highlighted that a percentage of patients remain uncontrolled in the post-operative phase despite optimal medical care and good compliance with local treatment.[18,27,38,39] In case of persistent uncontrolled CRSwNP, physicians need to explore the varying reasons for relapse or persistence which may be related to such factors as diagnosis, treatment, patient and surgery performed, before considering the next step of care for CRSwNP.[40] The goals of revision ESS should be carefully determined and may include the removal of obstructing polyps, addressing any residual anatomical issues that may contribute to recurrence such as scar tissue or insufficiently opened sinuses or the presence of complications such as mucocele formation. In the shared decision-making process, clinicians and patients must consider symptomatology, goals of the revision surgery, impact of the surgery on the patient (including the potential for an increased risk of intra-operative complications), post-operative compliance to anti-inflammatory treatment and the chronicity of the disease.[24,41]

Revision ESS can be more challenging than the primary surgery due to scarring and altered anatomy from previous procedures[42] resulting in a higher risk of complications,[43] and one can consider referring to a rhinologist or more experienced sinus surgeon. The surgeon must carefully assess the extent of inflammation, the extent of the surgery performed earlier, the presence of fibrosis and chronic osteitis and the potential impact on adjacent structures and include the higher complication risk in the decision process. This in turn may lead to a longer recovery period and higher indirect costs due to sick leave.[31,37,44]

5 | ASPIRIN TREATMENT AFTER DESENSITIZATION

Aspirin-exacerbated/non-steroidal anti-inflammatory-exacerbated respiratory disease (AERD/N-ERD) is a subset of CRSwNP characterized by severe CRSwNP, asthma and hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) (see Figure 4).

Aspirin treatment after desensitization (ATAD) is a specialized procedure designed to induce tolerance to aspirin and NSAIDs in AERD/N-ERD patients. It involves the gradual administration of increasing doses of aspirin under controlled conditions until the patient reaches a therapeutic dose. This process allows N-ERD patients to take aspirin safely and reach the potential anti-inflammatory benefits associated with its use.[45,46]

Aspirin treatment after desensitization has been shown to significantly reduce the size of nasal polyps in N-ERD patients.[47,48] The anti-inflammatory effects of aspirin contribute to reduced polyp burden and improved nasal airflow.[49] ATAD has also been associated with a reduction in asthma exacerbations and improved lung function in N-ERD patients with coexisting asthma.[50] Aspirin treatment

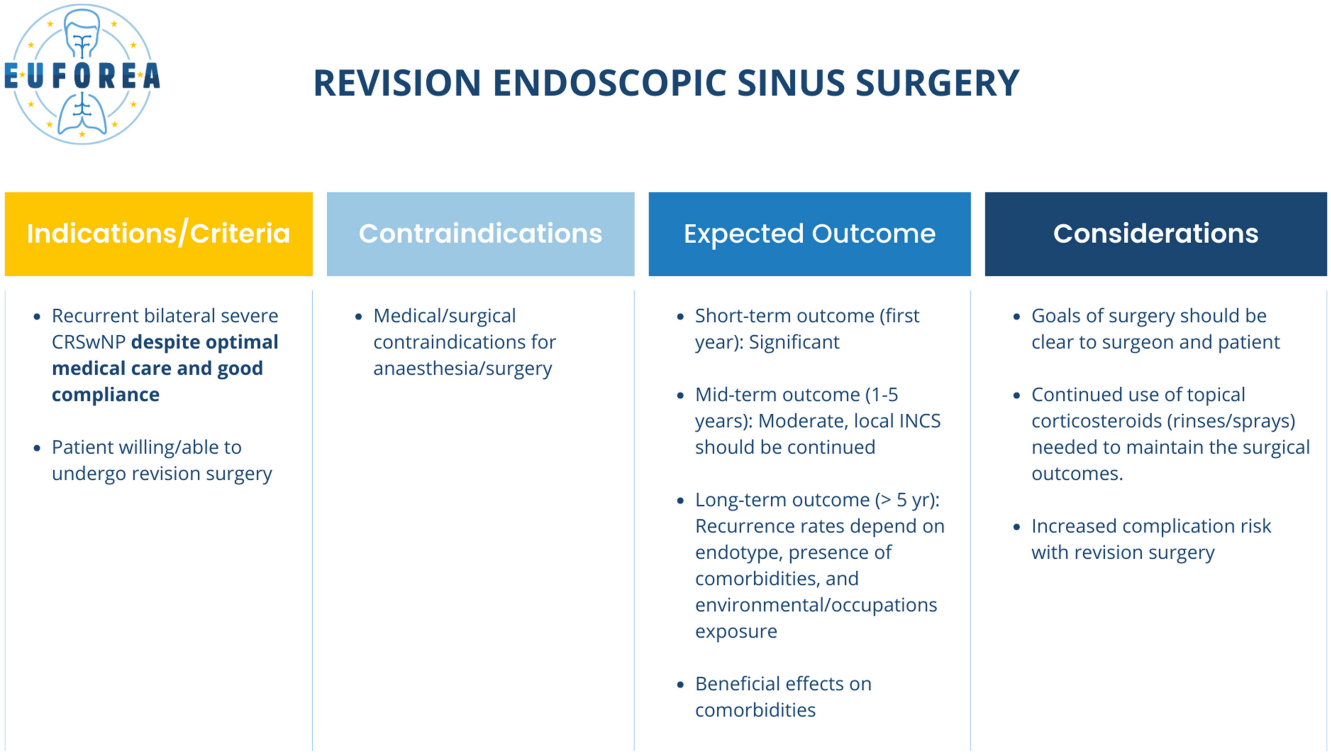

FIGURE 3 The indications/criteria, (relative) contraindications, expected outcomes and considerations when using revision endoscopic sinus surgery in the management of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP).

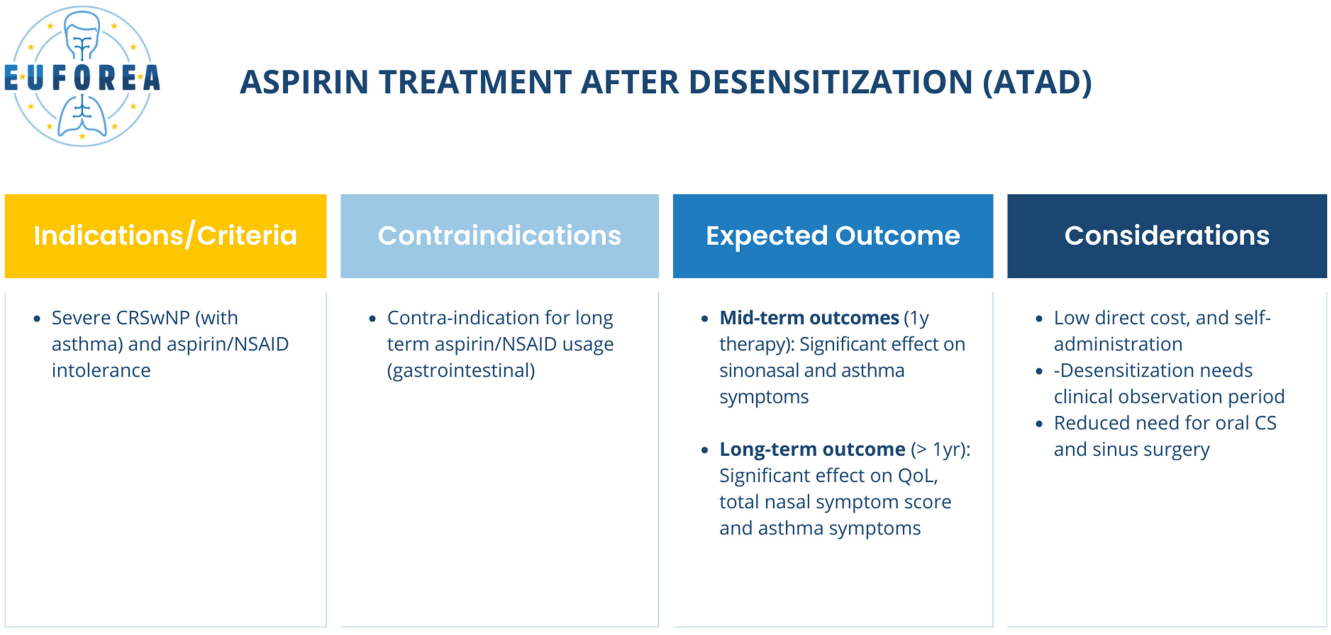

FIGURE 4 The indications/criteria, (relative) contraindications, expected outcomes and considerations when using aspirin treatment after desensitization (ATAD) in the management of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP).

may also improve the response of nasal polyps to corticosteroid therapy, potentially reducing the need for systemic corticosteroids.[47] Aspirin treatment may also improve the response of nasal polyps to corticosteroid therapy, potentially reducing the need for systemic corticosteroids.[47]

The EUFOREA's expert panel advises considering ATAD in patients with bilateral CRSwNP with comorbid asthma and history of aspirin/NSAID intolerance, especially when there is a need for aspirin-antiplatelet therapy or NSAIDs to treat chronic inflammatory conditions. ATAD is a therapy with a low direct cost and a significant

effect on patient's QoL, total nasal symptom score and asthma symptoms of the patient.[1,50]

Aspirin treatment after desensitization offers the most benefit in patients with recent debulking sinus surgery by preventing the recurrence of nasal polyps and reducing the need for SCS and ESS[51] but is associated with a risk of hypersensitivity reactions and/or gastrointestinal bleeding.[1] ATAD is a specialized medical procedure that demands careful oversight and management by an experienced healthcare provider.

After successful aspirin desensitization, close monitoring of patients is essential to ensure continued tolerability of aspirin and NSAIDs. Patients should be regularly assessed for symptom improvement, polyp recurrence and asthma control. Maintenance aspirin therapy is always required to maintain the desensitized state and its' anti-inflammatory benefits.

Aspirin treatment after desensitization is contra-indicated for patients with a severe hypersensitivity reaction after aspirin ingestion, i.e. an asthma attack, poorly controlled asthma (FEV1 <70%), pregnancy, history of eosinophilic oesophagitis, gastric and/or peptic ulcers or a history of bleeding disorders or coagulopathy.[47]

6 | BIOLOGICS

In recent years, there has been significant progress in understanding the underlying immune mechanisms that drive CRSwNP leading to the development of targeted biologic therapies (see Figure 5). For CRSwNP, biologics focus primarily on neutralizing specific pro-inflammatory type-2 cytokines, such as interleukin (IL)-4/IL-13,[52,53] or IL-5,[6,54,55] or mediators like IgE,[56] which are central in promoting the recruitment and activation of inflammatory cells in CRSwNP. By blocking the activity of these mediators, biologics modulate the immune response and reduce the chronic inflammation associated with the disease (including comorbidities).[57] Biologics have been shown to reduce the size of nasal polyps, improve nasal obstruction, relieve symptoms, improve the sense of smell and improve the quality of life.[48,58–61]

Based on EPOS 2020[1] and the EPOS/EUFOREA update on biologics 2023,[11] the EUFOREA expert panels recommend biologics in CRSwNP patients that are uncontrolled despite appropriate medical treatment and appropriate sinus surgery and who fulfil 3 of 5 criteria (presence of Type 2 inflammation, regular need for SCS/contra-indications to SCS, significant impact on QOL, loss of smell and comorbid asthma). Biologics are an effective treatment with an expected improvement in the short-term (16th week to 24th week), of at least one of the following symptom/scores: sense of smell, the nasal congestion score (NCS), the nasal polyp score (NPS), the Sino-Nasal Outcome Test (SNOT-22) and the visual analogue scale (VAS).[61–65] For dupilumab, long-term (up to 2 years) beneficial effects have been reported.[59,61] Beneficial effects on comorbidities may be confirmed at any point of the treatment, based on the aforementioned definitions and a reduction in the need for SCS and ESS can be observed.[66,67]

Biologics have a good safety profile but are contra-indicated in patients with hypersensitivity to the specific monoclonal antibodies or any drug components. Specific considerations should be taken in

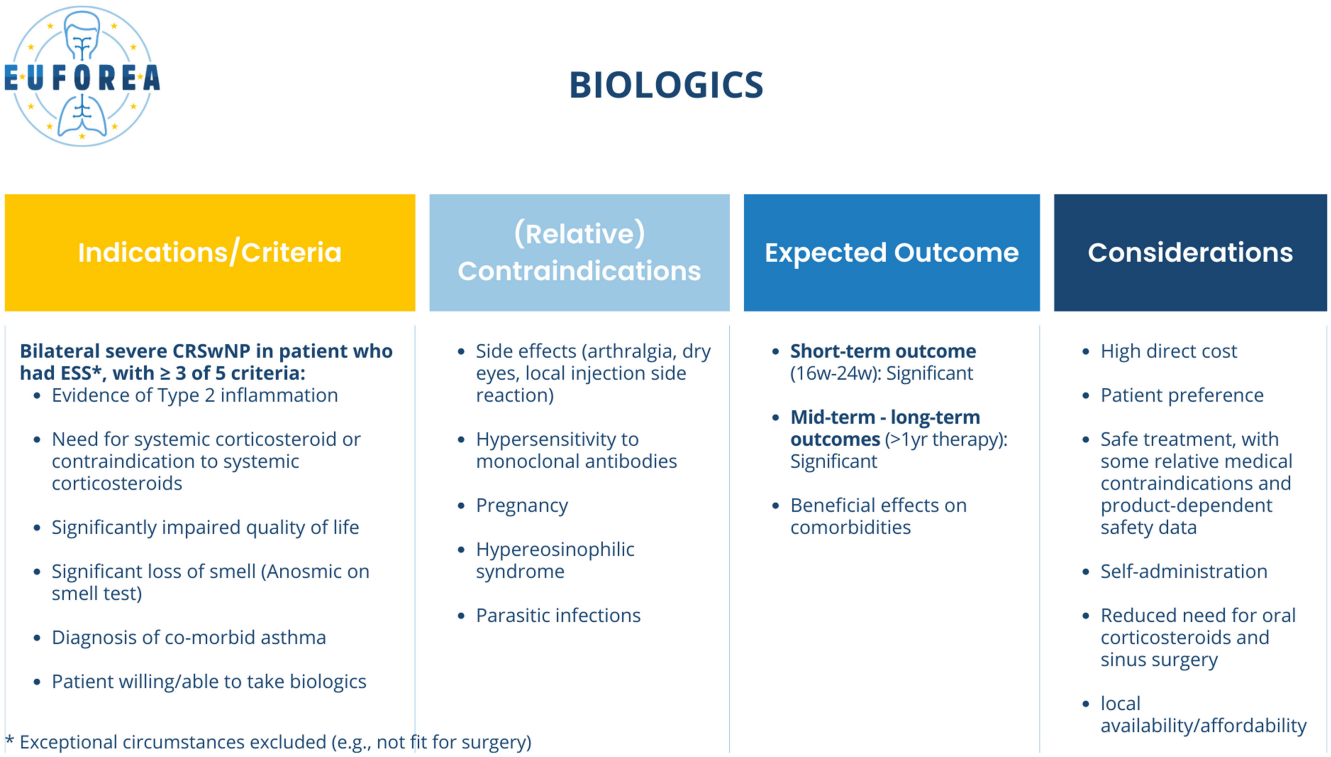

FIGURE 5 The indications/criteria, (relative) contraindications, expected outcomes and considerations when using biologics in the management of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP).

pregnancy since there is not yet enough data to rule out foetal harm or other side effects.[68,69] In this regard, the best data are available for omalizumab, where no increase in congenital anomalies has been demonstrated to date.[68–70] Therefore, the EUFOREA group advises to carefully counsel pregnant patients and female patients who wish to have children and to only continue the biologic if there are very strong reasons to do so.[68–70] Two other reasons to closely monitor patients/discontinue a biologic are hypereosinophilia (mainly dupilumab[71–73]) and helminth infections if patients do not respond to anti-helminth treatment.[74,75]

Overall, biologics are a safe and effective treatment option in most severe uncontrolled CRSwNP patients, with the need to properly select the patient given the high direct costs and the necessity of repeated self-administration.[48,59,61,76]

7 | CONCLUSION

This overview of treatment options for severe uncontrolled CRSwNP with indications and considerations for clinicians and patients aims to provide a further step forward in the personalization of care in CRSwNP. Ideally, patients can be offered the option of different strategies beyond SCS and primary/revision surgery, such as ATAD or biologic therapy, thereby benefiting from a personalized treatment plan.

AUTHOR CONTRIBUTIONS

PH and WF developed the first version of the manuscript. All authors developed, revised and critically reviewed the manuscript and provided final approval of the version submitted for publication. All authors participated in the development of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Isam Alobid: Consultant for Sanofi, Novartis, AstraZeneca, GSK, Viatris, Salvat, Storz, Olympus, Metronic, MSD and Roche. **Wilma Anselmo Lima:** No conflicts of interest to declare in relation to

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Advisory board at AstraZeneca, GSK and Sanofi. **Lisa Caulley:** No conflicts of interest to declare in relation to this initiative. **Adam Chaker:** Dr. Chaker reports grants, speaker honoraria, consultancy or advisory fees and/or research support and other all via Technical University of Munich from Allergopharma, ALK Abello, Astra Zeneca, Bencard/Allergen Therapeutics, GSK, Novartis, LETI, Roche, Zeller, Sanofi Genzyme/Regeneron, Thermo Fisher, European Institute of Technology (EIT Health) and Federal Ministery of Research and Education Germany. **Jannis Constantinidis:** Has received honoraria for consultancy from GSK. **Diego Conti:** No conflicts of interest to declare in relation to this initiative. **Eugenio De Corso:** Received fee for consultation, speaker activity, advisory board by Sanofi, Regeneron, GSK, Novartis and Astrazeneca. **Martin Desrosiers:** Received fee for consultation, speaker activity, advisory board by sanofi/Regeneron, GSK. Research support, sanofi/Regeneron, GSK. Equity holder, Probionase Therapies Inc. **Zuzana Diamant:** In the past 3 years, ZD received speaker or consultant honoraria and/or served on advisory boards at: Antabio, Foresee Pharmaceuticals, GlaxoSmithKline, Hippo-Dx, QPS-Netherlands, Sanofi-Genzyme-Regeneron, all outside the submitted work. From 2012 to 2020 she acted as Director Respiratory & Allergy Research at QPS-Netherlands; in 2019-ongoing, QPS-Netherlands received a European grant from ERA4TB (4 years) and funding from Foresee Pharmaceuticals for early respiratory studies. **W. J. Fokkens:** The department of Otorhinolaryngology of the Amsterdam University Medical centre, location AMC received grants for research in Rhinology from: ALK, Allergy Therapeutics, Chordate, Novartis, EU, GSK, MYLAN, Sanofi-Aventis and Zon-MW. 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