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Rhinology

Practical recommendations for managing severe chronic rhinosinusitis with nasal polyps in the era of biologics

Raccomandazioni pratiche nella gestione ambulatoriale della rinosinusite cronica con poliposi nasale severa, nell'era dei biologici

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SUMMARY

Objective. We conducted a national survey to understand how rhinology practice has changed with the advent of biologics and how this affected patients with uncontrolled, severe chronic rhinosinusitis with nasal polyps (CRSwNP). We aimed to analyse the results of the survey and infer practical recommendations for clinical practice.

Methods. A group of ear, nose, and throat specialists (ENTs) experienced in the management of CRSwNP developed a 74-question survey. ENTs from rhinology centres authorised to prescribe biologics in the context of the national health system were invited to answer it between 01/05/2022 and 31/07/2022. The responses underwent descriptive analyses, and the authors discussed the results and derived practical recommendations for clinical practice.

Results. ENTs working in rhinology centres changed their practices coinciding with the advent of biologics. CRSwNP evaluations have become more complex because they involve diagnostic confirmation, determining the patients' immunologic profile, and other factors. We observed heterogenous behaviours in practice that may be conditioned by the novelty of the topic. The results of the survey were used to develop practical recommendations for ENTs and are summarised herein.

Conclusions. Clinical practice in rhinology outpatient clinics has changed profoundly in the era of biologics. Our practical recommendations for clinicians working in rhinology centres are expected to help standardise practice and improve care.

KEY WORDS: biologics, practical recommendation, chronic rhinosinusitis, nasal polyps, Type 2 inflammation

RIASSUNTO

Obiettivo. *Abbiamo condotto un'indagine nazionale per capire come la pratica rinologica sia cambiata con l'avvento dei biologici e come questo abbia influenzato i pazienti con rinosinusite cronica grave non controllata con polipi nasali (CRSwNP). L'obiettivo è analizzare i risultati dell'indagine e dedurre raccomandazioni pratiche per la pratica clinica.*

Metodi. *Un gruppo di otorinolaringoiatri esperti nella gestione della CRSwNP ha sviluppato un sondaggio di 74 domande. Gli otorinolaringoiatri dei centri di rinologia autorizzati a prescrivere biologici nel contesto del sistema sanitario nazionale sono stati invitati a rispondere tra il 01/05/2022 e il 31/07/2022. Le risposte sono state sottoposte ad analisi descrittiva e gli autori hanno discusso i risultati e definito alcune raccomandazioni applicabili alla pratica clinica.*

Risultati. *Gli otorinolaringoiatri che lavorano nei centri di rinologia hanno modificato la loro routine diagnostica con l'avvento dei biologici. La valutazione della CRSwNP è diventata più complessa, perché implica la conferma diagnostica, la determinazione del profilo immunologico del paziente e non solo. Abbiamo osservato comportamenti eterogenei nella pratica che possono essere condizionati dalla novità dell'argomento. I risultati dell'indagine sono stati utilizzati per sviluppare raccomandazioni pratiche per gli otorinolaringoiatri e sono qui riassunti.*

Conclusioni. *La pratica clinica negli ambulatori di rinologia è profondamente cambiata nell'era dei biologici. Le nostre raccomandazioni pratiche per i medici che lavorano nei centri di rinologia dovrebbero contribuire a standardizzare le pratiche e a migliorare l'assistenza.*

PAROLE CHIAVE: *raccomandazioni pratiche, terapie biologiche, rinosinusite cronica, polipi nasali, infiammazione di tipo 2*

Introduction

The advent of biologics has caused a rapid and widespread change in the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) [1,2]. Consequently, the management of this condition, especially severe cases, has evolved in clinical practice [3]. The evaluation of CRSwNP is usually performed by collecting information via medical history and scoring tools to determine disease severity and level of control[4]. Notably, endo-phenotyping is particularly relevant prior to the initiation of biologics [5]. This will be even more important in the future, given that, in addition to the anti-IL-4/13 dupilumab, the anti-IgE omalizumab is now available for prescription and that Italian Medicines Agency (AIFA) has approved the anti-IL-5 agent mepolizumab for CRSwNP. However, the real-world utilisation of different diagnostics and their impact on the management of CRSwNP remain the object of discussion. Another aspect that should be investigated is the role of multidisciplinary referrals for this condition [5].

Although disease-specific consensus and protocols are widespread [5-11] to guide treatment with biologics, it is desirable to reach a national consensus on baseline and follow-up examinations to determine eligibility and assess response to biologic treatments. The use of biologics in

clinical rhinology practice, in fact, raises new issues such as the immunotyping and monitoring of specific parameters during treatment.
Therefore, we conducted a national survey to better understand how rhinology practice has changed with the advent of biologics and how this has affected the diagnostic and therapeutic journeys of patients with uncontrolled, severe CRSwNP in real-life. We then analysed the survey results and derived practical recommendations that can be useful in the management of these patients.

Materials and methods

We conducted a survey involving a representative sample of Italian ear, nose, and throat specialists (ENTs) managing severe uncontrolled CRSwNP working in rhinology centres authorised to prescribe biologics by the national health service. The survey was developed by a group of ENTs experienced in the management of CRSwNP that met remotely to discuss the aspects that should be included in the questionnaire. The authors were divided into groups and proposed questions for specific survey topics related to routine practical management of CRSwNP. Next, a selection process with critical appraisal of all questions took place (by EDC, EC, CP). Finally, a remote approval by all authors produced a total of 74 questions that were formatted for style and answer possibilities to ensure direct and standardised responses that reflect the respondents' experience. The full questionnaire and the complete responses are available in the supplementary file.
Thanks to the collaboration of the members of the Italian Committee for the use Biologics in Rhinology centres authorised to prescribe biologics for severe uncontrolled CRwNP were identified in each region. The survey was set up on Survey Monkey® and was sent by email to one of the prescribing doctors at the centre. No information about the participants was collected in order to keep the results of the questionnaire anonymous. We received questionnaires from throughout Italy without a significant discrepancy between the north, center and south. The survey distribution started on May 1st, 2022 and was closed on July 31st, 2022. All answers were considered appropriate and were included in the analysis.
We performed a descriptive analysis and presented some of the most significant results as histograms. The members of the Joint Committee on Biologics in Rhinology and of the Italian Rhinology Committee of the Italian Society of Otorhinolaryngology discussed the results of the survey and compared them with current guidelines, and especially EPOS 2020. For this purpose, we compared what was reported in the EPOS 2020 with what was found in practice (Tabs. I, II). Practical recommendations were written and submitted for review and approval by all the members of the committees. All the changes made were discussed and refined until unanimous approval was obtained.

Results and practical recommendations

Epidemiological data of the respondents
A total of 61 ENTs working in rhinology centres authorised to prescribe biologics responded to the survey. Most were endoscopic sinus surgeons (92%), 57% worked in university hospitals and 43% in public hospitals. Before the inclusion of biologics in clinical practice, a second-level rhinology clinic was present in almost half of the facilities and within a multidisciplinary network (46%), whereas in 28% it existed without a multidisciplinary network; in the remaining, the clinic and multidisciplinary network were created after the approval of biologics for CRSwNP; currently, it is well structured in 70% of cases as shown by Q1-9 in the supplementary file (s.f.).

Defining type 2 inflammation in biologic therapy candidates (Q10-31 s.f.)
From the results of this section, some discrepancies between theory and practice are evident. Respondents appear aware of how and what to answer, but clinical practice questions remain challenging. Although ENTs know the theoretical concepts, in practice many things are difficult to implement from a management point of view. Complete blood counts (CBCs), for example, are considered useful by survey respondents to define the inflammatory profile of CRSwNP patients (88% agree) (Q10 s.f.). Nevertheless, 77% of participants "always" check CBCs prior to considering biologics (Q11 s.f.). Unfortunately, this means that 23% of respondents do not routinely check CBCs to define the inflammatory profile of CRSwNP patients prior to initiating a biologic, indicating that education in this aspect may be needed since CBCs are affordable and useful when they are put in the patient's clinical context [12-14].
Regarding the use of follow-up CBCs during biologic treatment for CRSwNP, almost half (45%) of the respondents perform these tests every 3 months, over a third perform them bi-monthly or monthly (15% and 22%), and fewer (15%) perform them every 6 months (Q12 s.f.).
Similarly, most respondents are aware of the importance of IgE in defining type 2 inflammation as suggested by the literature [15,16], even if less than half of patients have total blood IgE routinely measured. In fact, most respondents (82%) agree that measuring total immunoglobulin E (IgE) is useful to define type 2 inflammation (Q14 s.f.), although only 47% request total blood IgE in practice (Q15 s.f.). Likewise specific IgE levels are not routinely measured in practice (Q16 s.f.).

Other notable discrepancies between theory and practice include histopathological analysis. For instance, 58% of respondents believe that definitive histological analysis of the polyp may be useful (Q25 s.f.), but the vast majority (75%, Q27 s.f.) never or only rarely perform a biopsy to define the endotype.

Regarding the cut-offs indicative of type 2 CRSwNP, there is no agreement in practice about blood eosinophil (Q13 s.f), IgE levels (Q17 s.f.), or eosinophil count at histologic findings (Q28 s.f.). Therefore, we propose referring to levels suggested by international guidelines (total IgE ≥ 100 U.I./ml; blood eosinophil count ≥ 250 cell/µl, local eosinophil count > 10/hpf) [2,17].

From the results of survey, it emerged that clinicians do not consider other biomarkers to be clinically useful (Q18 s.f.) with the purpose to define type 2 inflammation. Even though biomarkers have been widely discussed in the literature [18-21], there was no agreement among the respondents about those that can be useful in practice and most focus their attention on interleukin-5 and interleukin-4, probably due to the new treatment possibilities that biologics provide [22].

Another notable point is that there is no agreement about when to request CBCs during biologic treatment. Currently, the majority of respondents request CBCs every 3 months, while others do it every 6 months thereby risking to bypass the phase of transient increase in eosinophils that some patients may experience with certain biologics. Additional literature is needed to establish the importance of performing CBCs during biologic treatment and if the timing can be influenced by the type of biologic used (Q12 s.f.).

Through the survey, we also sought to understand whether other modalities are used in practice to define type 2 inflammation. Interestingly most respondents (87%) agreed that allergy evaluation and related immune-allergology tests are important to define CRSwNP endotypes (Q19 s.f.) and almost 73% of them request immune-allergology tests all the time or often in practice (Q20 s.f.). On the other hand, although studies [5,23] show that the definition of local inflammation may be useful in definition of the endotype, it is not always characterised in clinical practice. Almost 70% of respondents agreed that cytologic examinations via nasal scraping (standard lower turbinate method) may be useful to define the local inflammatory profile (Q21 s.f.), although only 50% perform nasal cytology routinely (Q22 s.f.) and there was no agreement about the level of local eosinophil counts indicative of type 2 inflammation; only 32% indicated a count > 10 cells/field (Q23 s.f.). Almost two-thirds of respondents were uncertain or disagreed when asked if nasal cytology should be performed via other methods (middle turbinate or lateral nasal wall), while a third thought those options were acceptable (Q24 s.f.). Only 12% reported they perform nasal polyp biopsies to define type 2 inflammation (Q27 s.f.). Respondents, in fact, declared that in practice the information that they can get from histopathological examinations may largely vary, in 35% of the centres the type of inflammation is not specified and the presence of eosinophils is neither reported nor quantified (Q26 s.f.).

Finally, 59% of respondents agreed that fractional exhaled nitric oxide (FeNO) may be helpful to define inflammatory profile of CRSwNP, but only 25% requested it in daily practice (Q30 s.f.). Our data demonstrated that most respondents had no experience with FeNO, did not request it, or did not know about it (Q31 s.f.).

Measuring disease severity in CRSwNP candidates for a biologic (questions 32-37 s.f.)

The survey shows that tools to measure disease severity are used in routine practice and specifically the surveyed ENTs consider Quality of Life (QOL) questionnaires, CRSwNP extent measured by Nasal Polyp Score (NPS) or Computed Tomography (CT) scan and comorbidity assessment. Figure 1 (Q32 s.f.) shows the most used tools to determine disease severity in CRSwNP candidates for biologics. In terms of symptoms evaluation and the burden on QOL, almost all respondents (98%) use the sino-nasal outcome test 22 (SNOT-22) (Q34 s.f.) confirming its validity as demonstrated in the literature [6,24,25]. Notably, over 70% of respondents use the visual analogue scale (VAS) (including nasal obstruction, rhinorrhoea, smell, and craniofacial pain). This scale allows investigating specific rhinology symptoms, giving more weight to the nasal domain than to the entire SNOT-22. This scale is probably frequently used due to its simplicity and speed of execution as suggested in guidelines [26]. In comparison, the nasal congestion score (NCS) and total composite symptoms score (TCSS) are rarely used (25% and 11%), even though most monoclonal antibody studies and some guideline recommendations are based on this score [6].

Furthermore, analysing clinical history of the patient, ENTs consider previous surgery (86%) more relevant than the need for previous oral corticosteroid (OCS) cycles (66%) (Q33 s.f.). Only a minority of respondents considered the total dose of OCS (41%) and the total days of OCS (30%) used in the previous year. We believe that the importance of corticosteroids during disease control should be emphasised as suggested in our previous experience [14,32]. The evaluation of disease control should be performed as well including surgical and medical treatments, especially steroids.

In terms of instrumental scores, the NPS seem to play a prominent role in assessing disease severity via endoscopy in practice, and is the most widely used (98%) endoscopic score (Q35 s.f.).

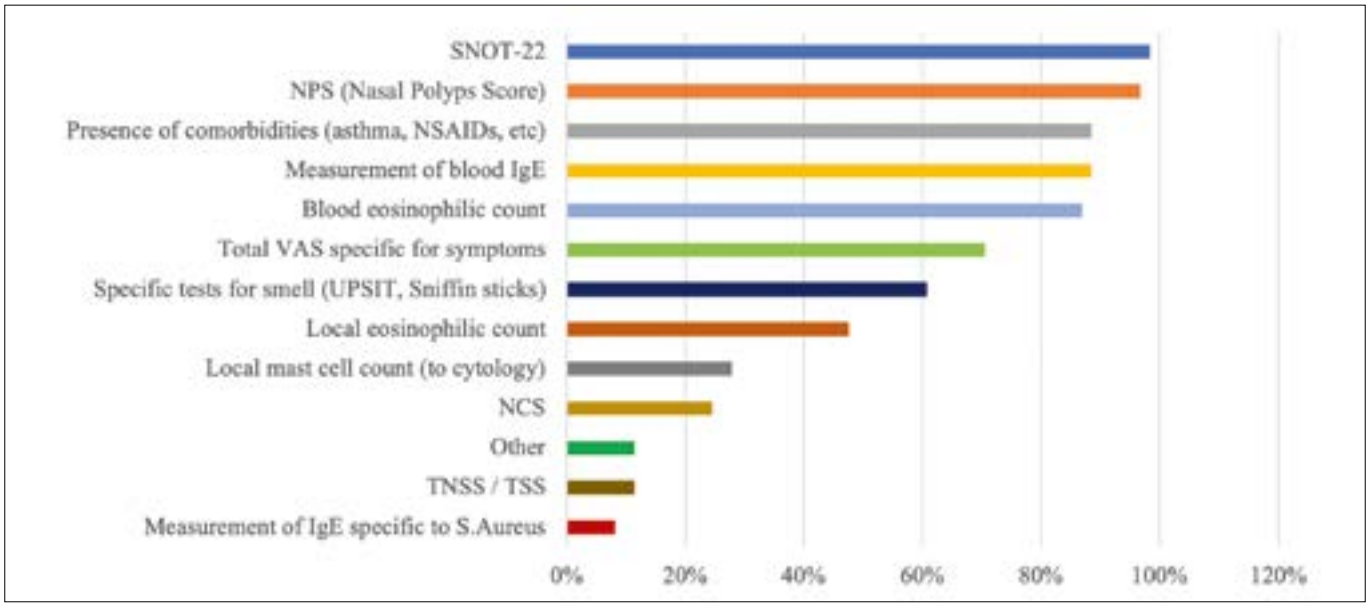

Figure 1. Scores or elements used in clinical practice to establish disease severity (Q32 s.f.). SNOT-22: sino-nasal outcome test 22; NSAIDS: Nonsteroidal anti-inflammatory drugs; VAS: visual analogue scale; UPSIT: University of Pennsylvania Smell Identification Test; NCS: nasal congestion score; TNSS: total nasal symptom score; TSS: total symptoms scores; S: staphylococcus.

The reason for this probably lies in its use in registration trials, biologic therapy guidelines, and regional therapeutic plans [27-29]. Regarding CT scans, we observed that participants use them for diagnostic purposes, differential diagnosis, and for surgical planning (Q36 s.f.). However, only 56% of ENTs use the Lund-Mackay score to assess the extent and severity of disease even if high values indicate a greater risk of future relapse [30]. Other reasons to perform CT scans were to confirm CRSwNP diagnoses (localised or diffuse), for surgical planning, and differential diagnoses.

Interestingly, participants also consider haematologic markers such as eosinophilia (87%) and total serum IgE (89%); in addition, type 2 comorbidities are considered predictive of severity by 89% of ENTs. Local eosinophilia is considered only by 48% of respondents by cytology or histology. The role of blood eosinophilia and the presence of type 2 comorbidities is noteworthy and in full compliance with the literature [33,34]. Surprisingly, less than half of the respondents assess local eosinophilia, although the scientific evidence confirms its correlation with disease severity [16,18,21,35-37] and even more compared with blood eosinophilia. Further studies are necessary to better define how the evaluation of local inflammation with the available methods may impact definitions of disease severity. The current literature is probably not sufficient to strongly influence clinical practice.

Lastly, there is a final aspect that we would like to highlight, namely nasal flow is not often objectively evaluated in practice to assess disease severity. Indeed, only a quarter of ENTs (26%) perform an active anterior rhinomanometry and only 11% perform peak nasal inspiratory flow (PNIF) at the first visit (Q37 s.f.). This is probably because rhinomanometry is costly and time-consuming, while PNIF (positive nasal inspiratory flow) is not a widely spread tool due to limited experience, even though it is a quick, affordable option, and could easily and satisfactorily be used in clinical practice [31]. Nasal obstruction is one of the major symptoms of CRSwNP, and based on our results its evaluation is probably underestimated in practice. We believe that its assessment is important to obtain an idea of severity of the disease. For this reason, not only VAS nasal obstruction but also NCS and PNIF, due to their simplicity, may be helpful to enhance its evaluation in practice [31].

Measuring the sense of smell in biologic therapy candidates (questions 38-41)

Even though olfactory assessments prior to biologic treatment initiation seem to be very important as suggested by several guidelines [2,5,17,25], the survey clearly shows (Q38 s.f.) that olfactory function measurement is less common in practice [38]. Indeed, only 53% of respondents agreed that performing olfactory tests is essential before initiating biologic treatments in CRSwNP patients, and 13% stated that testing is necessary only if patients report anosmia or hyposmia. Moreover, to the same question, 24% declared they did not perform olfactory tests because they are not avail-

able in their outpatient clinic, and 7% considered it was not necessary (Q38 s.f.). When asked about the method used to measure olfaction, most reported they use an olfactory test (Q39 s.f.), and in particular an olfactory identification test, but a large proportion also use VAS smell (Tab. I). Not surprisingly, the 16 odours SS identification test is the method of choice to evaluate olfaction. This test is in fact simple, fast, and an easy method to measure the sense of smell [39]. Thus, considering the usual distribution of people with normal olfaction and anosmia, an identification test with 16 odours allows appropriate discrimination between anosmia and normosmia and the interpretation of intermediate results (hyposmia) is acceptable [4].

Interestingly, over a third of the respondents (38%) reported that they use a VAS for smell dysfunction to determine olfaction in CRSwNP patients. However, although VAS for smell is a validated quantitative method, self-evaluation of olfactory function does not correlate with measured olfactory function [40]. This is because patients and their physicians can be completely unaware of their impaired sense of smell unless it is measured [4]. Furthermore, in patients complaining of hyposmia, the extent of dysfunction can be misevaluated if only questionnaires are used. The inability of patients to self-rate their olfaction is well-known (30-40% of CRS patients with impaired olfactory function rate themselves as unimpaired, and only 27% can accurately report

Table I. Comparison of EPOS guideline indications and those adopted in real-life regarding definition and measurement of CRS severity and features.

	EPOS2020 guidelines [25]	Italian real-life practice (% of responders)
Definition of type 2 inflammation	The EPOS2020 steering group was unclear as to whether it was essential to measure total IgE either at initial presentation of CRS (10% agreed) or after failure of appropriate medical or surgical treatment in ENT (48% agreed)	Most respondents (82%) agree that measuring total immunoglobulin E (IgE) is useful to define type 2 inflammation although only 47% request total blood IgE in practice
	EPOS2020 suggested as serum IgE cut off to define type 2 inflammation: Total IgE > 100	Only 37% consider IgE > 100 indicative of type 2 inflammation in practice
	The EPOS2020 steering group was unclear as to whether it was essential to evaluate blood eosinophilia either at initial presentation of CRS (17% agreed) or after failure of appropriate medical or surgical treatment (59% agreed).	In practice, 88% agree that complete blood counts (CBCs) are useful to define type 2 and 77% of participants check CBCs prior to considering biologics
	EPOS2020 suggested as cut off (EOS > 250/ul)	In practice only 45% of respondents consider EOS > 250 /ul as indicative of type 2 inflammation
	The EPOS2020 steering group did not consider it is essential to do histopathology / biopsy at initial presentation of CRS (13%) and responses were unclear after failure of appropriate medical or surgical treatment (31%)	58% of respondents believe that biopsy may give information on inflammatory profile of CRS patients but only 12% perform it in practice
	EPOS 2020 suggested the cut off (EOS > 250/ul) 10 cell /hpf as indicative of type 2 inflammation	42% believe that tissue eosinophilic count value: > 10 cells/hpf is indicative of type 2 inflammation
Measurement of disease severity/ control	Expert committee proposed to combine severity of symptoms, aspect of mucosa and medical intake as parameters of control. CRS control test takes into account presence and severity of four major sinonasal symptoms (VAS > 5), sleep and/or fatigue, endoscopic evaluation and need for oral medication. Core outcomes set: Need for systemic medication (steroid or antibiotic); Progression to surgery; Lund-Kennedy score	Parameters used in practice to establish non-disease control: (Q33) No. short cortisone cycles in last year 66% Total dose of cortisone in the last year 41% Total days of cortisone intake in the last year 29% No. previous surgeries 87% Recurrence time since last surgery 77%
	EPOS2020 steering group proposed as important issue to be considered for indication to biologics assuming that they suggest a severe disease: SNOT-22 > 40, Anosmia at smell test, presence of comorbidities. The authors also suggested that a VAS > 7 was indicative of severity	Scores used in measuring disease severity in practice: NPS 97%, SNOT-22 98%, total VAS 70%, NCS 25%, smell tests 61%, presence of comorbidities 89%
Measurement of smell	EPOS2020 steering group unclear if essential to do smell test in CRS after failure of treatment	58% believe is essential to use olfactory test before starting treatment with biologicals but in 23% depends on the availability of the olfactometric test
	EPOS2020 steering group suggested to assess smell through testing, not VAS	Tools used to evaluate olfaction in practice: (Q39), VAS olfaction 38%, Sniffin' Sticks 35% UPSIT 10%

EPOS2020: European Position Paper on Rhinosinusitis and Nasal Polyps 2020; CRS: Chronic rhinosinusitis;SNOT-22: sino-nasal outcome test 22; EOS: eosinophilia; VAS: visual analogue scale; UPSIT: University of Pennsylvania Smell Identification Test; NCS: nasal congestion score; NPS: nasal polyp score; VAS: Visual: visual analogue scale.

their olfactory ability) [40]. Accordingly, in a recent study of the olfactory performance of CRSwNP patients before and after biologics, the authors [41] observed that patients reported a higher degree of improvement of smell dysfunction on the VAS than on tests for smell identification, demonstrating that the patients were not aware of the degree of their olfactory dysfunction. This observation would demonstrate the partial unreliability of VAS alone and the need to always perform an olfactory test, at least for smell identification. For this reason, we suggest that olfactory tests should be used in association to subjective methods [42].

Regarding how to measure olfaction during biologic treatment (Q40 s.f.), over two-thirds of respondents (68%) use semi-objective olfactometry tests, 47% use VAS for olfaction, and only 13% do not see the need for olfactometric testing. Close to a third evaluate sense of smell every three months or at every follow-up (35% and 32%)(Q41 s.f.). The fact that some of respondents consider olfactory dysfunction evaluation not necessary before starting biologics (11%) and during the therapy (13%) is not acceptable. This is noteworthy because smell impairment is one of the key factors in determining disease severity and severity of olfactory loss is known to be parallel to the severity of inflammation in CRS patients. Therefore, using simple methods to measure olfaction during follow-up can help to assess response to treatment.

In conclusion, although olfactory threshold tests are more precise than suprathreshold olfactory identification tests [40,42], we believe that since quick and affordable tests are needed, smell evaluation prior to biologics in CRSwNP patients and during follow-up can be assessed with tests for smell identification (16 or 12 odours SS identification test) together with subjective methods (VAS for smell) that provide important information about olfaction and inflammation status [4,42].

Practical management of asthma patients with CRSwNP (Q42-47 s.f.)

Our data show high levels of multidisciplinary collaboration between pulmonologists and ENTs in these complex comorbid patients (Q47 s.f.). Our data shows that 92% respondents have a good experience in evaluating comorbid patients because they work in centres where there is already an established medical pathway for severe asthmatic patients (Q42 s.f.). A minority not working in centres with specialised asthma clinics may have less experience with biologics, since they have not worked previously with these therapies in direct contact with pulmonologists.

Although baseline rhinology assessments of severe asthma patients prior to initiating biologics are common according to most respondents (Q42 s.f., 92%), pre-established rhinology follow-ups during biologic therapy are not routinely planned for asthmatic patients (88%) (Q43 s.f.). Instead, they are requested on demand depending on nasal symptoms (22%), previous history of rhinology pathologies (51%), or for patients with a diagnosis of CRSwNP (15%) (Q43 s.f.).

On the other hand, respondents carefully evaluate their patients with severe asthma and CRSwNP from a pneumological point of view, especially to obtain information about duration of biologic therapy, asthma control, and endotype (Q44 s.f., 60-94% of respondents). Notably, 60% consider it is essential to share information with pulmonologists about asthma control prior to biologic therapy initiation (Q47 s.f.), although only 35% of ENTs are aware of specific assessment tools for asthma control (Q45 s.f.).

Regarding OCS (Q46 s.f.), ENTs often (81%) evaluate the amount of OCS their patients take for asthma. They recognise that this is useful to make in-depth evaluations with relevant indicators (54%), to record systemic OCS doses relative to their condition (19%) and to assess endocrine side effects (9%). Only 19% reported that OCS intake is difficult to quantify or that it is unnecessary (Q46 s.f.).

Asking for specific information about multidisciplinary team meetings (MDT), structured multidisciplinary meetings before patients initiate biologics take place in only 25% of rhinology centres (Q47 s.f.). We suggest that rhinology centres where patients with uncontrolled, severe CRSwNP are followed should establish direct collaborative networks with pulmonologists to facilitate pathways and to jointly discuss candidates for biologics. Structured multidisciplinary boards may be helpful in clinical practice to discuss and quickly share information about candidates for biologics [23,43-45].

Interestingly, our data demonstrate that ENTs concentrate more on correct asthma diagnosis, level of control, and previous and ongoing treatments (including systemic corticosteroids) than on comorbidities. This overlaps with the findings of our recent national survey [32], where ENTs reported that they pay more attention to previous need of systemic steroids for CRSwNP and where we suggested that the dosage of systemic steroids used for asthma should also be considered.

Practical management of severe CRSwNP patients naïve to surgical treatment (Q48-53 s.f.)

Our data suggest that the baseline clinical evaluations of severe CRSwNP patients naïve to surgery become more complex to perform compared to the past because an additional work up is now suggested by international guidelines. Figure 2 (Q48 s.f.) shows the tests that respondents consider necessary prior to surgical referral or biologic ini-

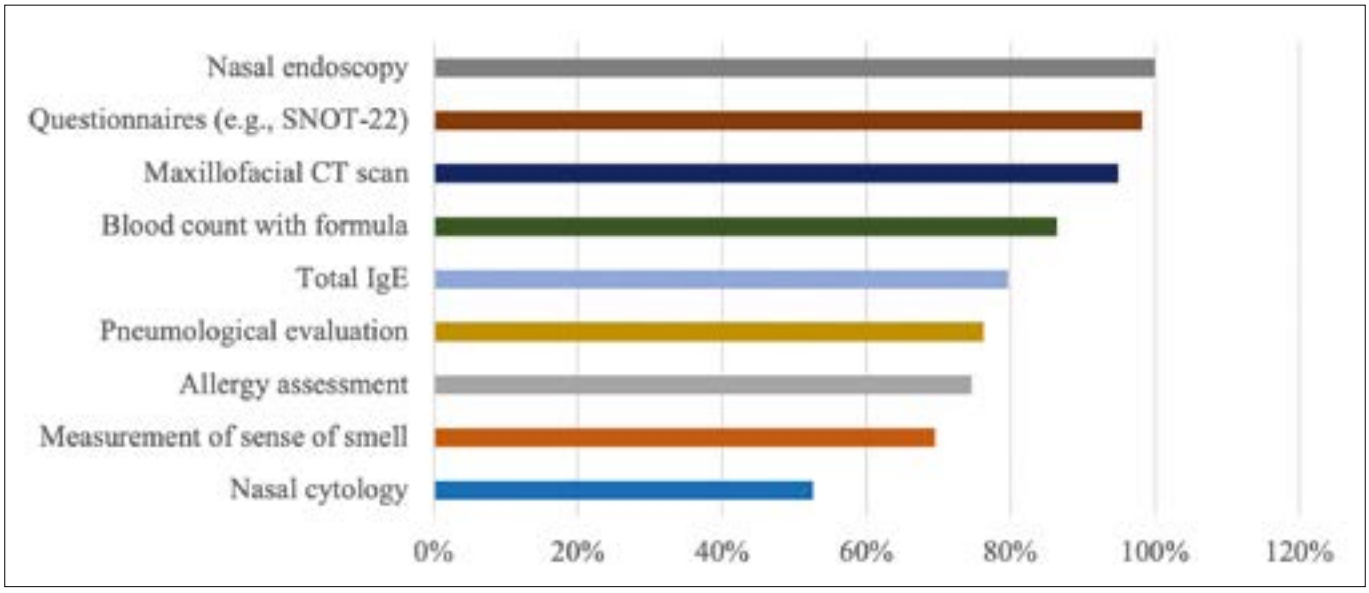

Figure 2. Tests and evaluations considered necessary for a patient with moderately/severe CRSwNP who has never been operated on and has never taken biological therapy (Q48 s.f.). SNOT-22: sino-nasal outcome test 22.

tiation. Most (> 90%) confirm diagnosis with maxillofacial CT scans, nasal endoscopies, and also administer QOL questionnaires. If local corticosteroids had never been prescribed (Q49 s.f.), ENTs usually suggest a course of these drugs with reassessment to evaluate efficacy over time. Blood tests during the first evaluation are frequently required, especially blood counts (86%) and total IgE (80%) (Q48 s.f.). Allergology and pneumology evaluations are also considered if never performed before (Q52 s.f.). Our results demonstrate that Italian ENTs are well-trained in diagnosing patients with nasal polyps and use additional evaluations. Most seek to confirm the diagnosis and assess type 2 inflammation by ordering eosinophils and total IgE levels at first evaluation. This may be due to the educational initiatives on biologics promoted by the Italian Society of Otolaryngology over the past two years [2,5,32,46]. Respondents are inclined to refer CRSwNP patients to allergology and pneumology specialists for further evaluation. However, more than half refer them to a pneumologist only when asthma is already diagnosed or strongly suspected. We believe that a practical compromise could be to routinely perform multidisciplinary evaluation in severe cases and in the presence of suggestive pulmonary symptoms in moderate or mild cases [2].

Regarding the indication of biologics to treat naïve patients, most respondents (Q53 s.f.) would prescribe first-line biologics only if there is a real contraindication to surgery (68%) as suggested in guidelines [25]. Notably, 15% of respondents always recommend surgery in naïve patients and a minority referred that it could be considered in case of categorical refusal of surgery by the patient and in the presence of poor prognostic indicators (Q53 s.f.).

Basing on current evidence, we believe that a first surgery should be skipped only if there is a real contraindication to it. It is still controversial if there could be a small window for drugs in naïve patients with clear risk factors for post-surgical recurrence [5]. Clinician attitudes may evolve in the future regarding first-line treatments for a specific subset of non-operated patients, but the current evidence does not support this strategy [47].

Practical management of CRSwNP patients that have undergone surgery but are naïve to biologics (Q54-57 s.f.)

Regarding CRSwNP patients who have undergone functional endoscopic sinus surgery (FESS) and are being considered for biologics, only 36% are routinely assessed with CT scans, and 51% only if needed for specific reasons (Q54 s.f.). From these results, it emerged that ENTs respondent to this survey do not routinely use CT scans when re-evaluating patients after surgery, especially if relapsing. Furthermore, they seldomly consider quantifying the extent of previous surgery (23%) (Q54 s.f.). Notably, our data show that respondents do not use specific scores to evaluate the adequacy of previous surgeries [48]. For example, 63% of respondents do not use the Amsterdam Classification of Completeness of Endoscopic Sinus Surgery (ACCESS) [48] score to evaluate the extent of the surgery (Q55 s.f.). Finally, our data suggest that the majority of the respondents do not know how to use ACCESS to decide between surgi-

cal revision over medical/biologic therapy (Q56 s.f.). There may be several reasons for this reluctance: Italian ENTs may not know this score since it has recently been introduced and since most ENTs have personally operated on their patients, they may not see the need for routine CT assessments. It is hard to interpret the answers for cases when ACCESS is used (Q56 s.f.) because of the paucity of responses [49].

When CRSwNP recurs post-endoscopic surgery (Q57 s.f.), the choice of biologics rather than surgical re-intervention may be challenging, especially if the previous surgery was insufficient (i.e., simple polypectomy without ethmoidectomy). In this situation, different factors (inflammation level, endotype) may be influential, and it may be difficult to establish how much the technical aspects of the surgery are involved. In this context, we encourage the use of specific assessment tools such as the ACCESS score, which may be useful to determine the completeness of the previous surgery (Q55 s.f.) [50]. The fact that the respondents seldomly use ACCESS indicates a need to provide education about the usefulness of this score.

The literature provides information on how to determine in which patients surgery may not guarantee control of the condition based on timing of recurrence. When considering another surgery, the data indicates that patients recurring within 3 years have poorer prognoses. Coincidentally, the respondents mostly answered that early recurrence (within one year) suggests biologics over surgical treatment [51] (92%) (Q57 s.f.).

Practical management of CRSwNP patients initiating and during biologic therapy (Q 58-62 s.f.)

The responses demonstrate a relatively homogenous approach for rhinology assessment of these patients. As shown in Figure 3 (Q58 s.f.), all the ENTs surveyed perform nasal endoscopies (rhinofibroscopies) prior to initiating biologics. Other tests commonly performed are eosinophil count (95%), total IgE (85%), maxillofacial CT scans (71%), and olfactometries (64%). Almost half (47%) of respondents also evaluate nasal cytology and only a few (15%) assess PNIF. Other blood tests are used by a minority of clinicians. Similarly, pulmonary inflammation assessments via FeNO are performed only by 10% of ENTs.

For evaluation of response, the parameters used during the first year of follow-up include QOL assessments via SNOT-22 by 100% of respondents, while only one-third (34%) use the NCS. Over half of respondents (53%) perform olfactometric assessments, while a minority of ENTs perform pneumology tests (FeNO, 5%; spirometry, 17%). Eosinophilia is evaluated through blood count by 80% of ENTs and blood chemistry tests by 39%(Fig. 4) (Q61 s.f.). All ENTs assess response to biologic treatment at 12

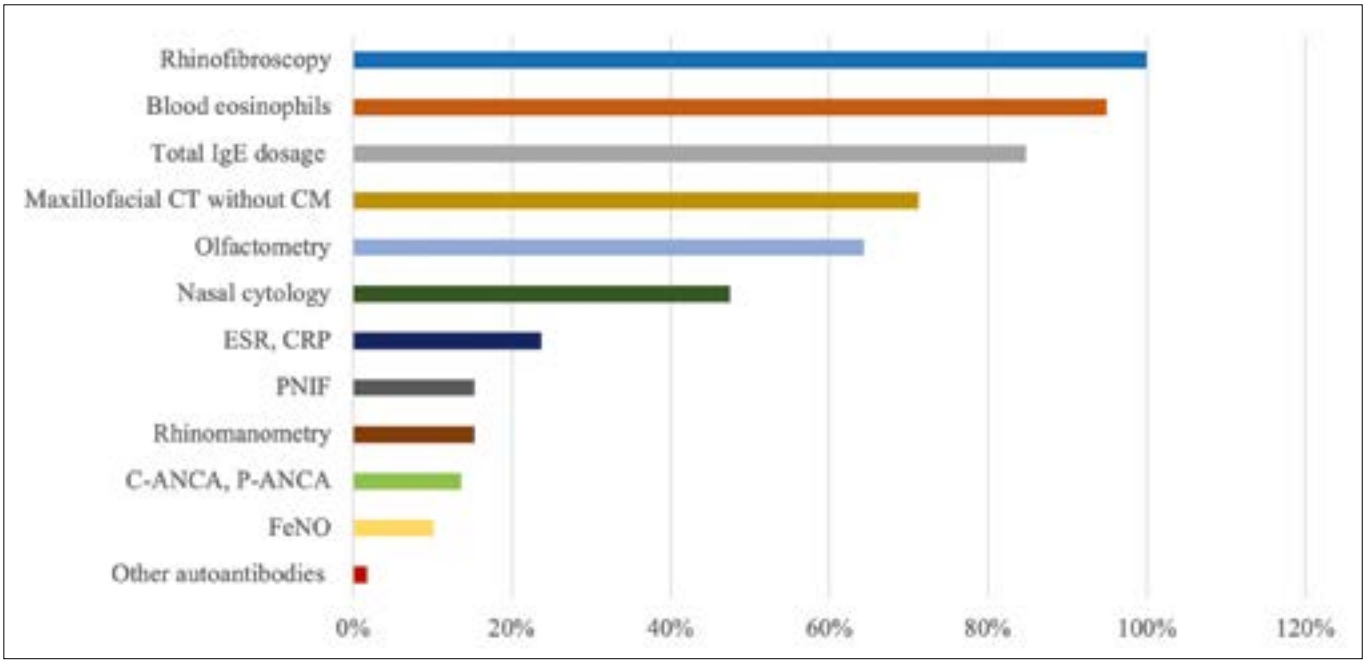

Figure 3. Evaluations deemed necessary to consider a patient with CRSwNP ready to initiate therapy with a biologic (Q58 s.f.). CM: contrast medium; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PNIF: peak nasal inspiratory flow; C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibodies; P-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; FeNO: fractional exhaled nitric oxide.

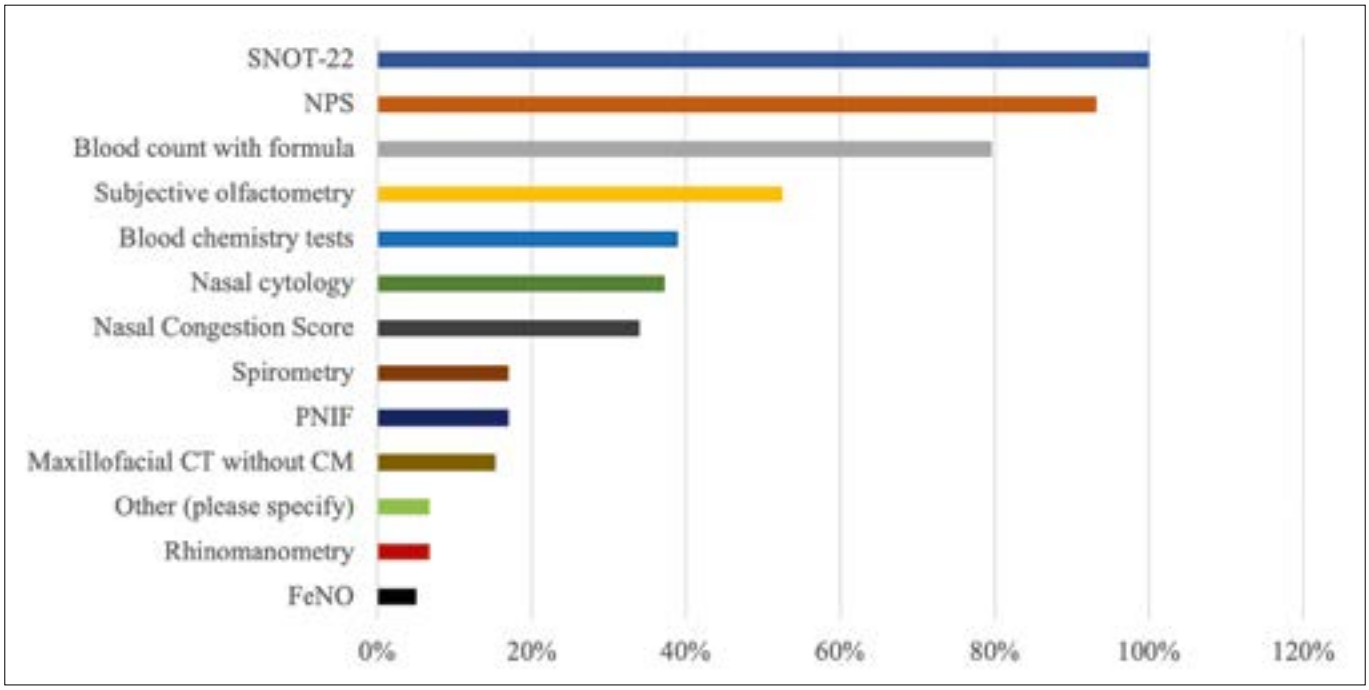

Figure 4. Parameters used in clinical practice in the first year of treatment during follow-up visits (Q61 s.f.). SNOT-22: sino-nasal outcome test 22; NPS: nasal polyp score; PNIF: peak nasal inspiratory flow; CM: contrast medium; FeNO: fractional exhaled nitric oxide.

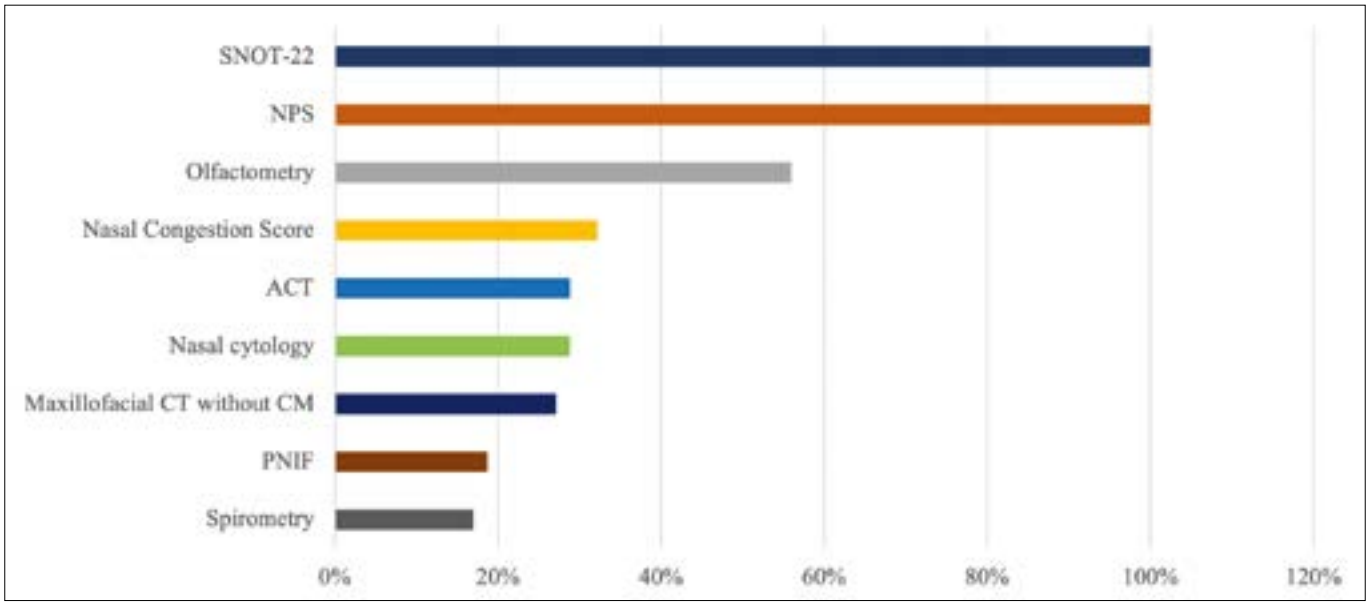

Figure 5. Parameters used to establish the response of biological therapy at 12 months (Q62 s.f.). SNOT-22: sino-nasal outcome test 22; NPS: nasal polyp score; ACT: asthma control test; CM: contrast medium; PNIF: peak nasal inspiratory flow.

months mainly via NPS and SNOT-22 (Fig. 5, Q62 s.f.). It is necessary to emphasise that in clinical practice, Italian colleagues seem to give equal importance to NPS. Real-world data may help this perception to evolve and change the use of this test towards a more cautious interpretation of NPS as it does not always correlate with improvements in smell and SNOT-22 [41]. Furthermore, more attention should be given to evaluating the sense of smell, improving comorbidities, and reducing corticosteroid intake according to EPOS guidelines.

Regarding the timing of follow-up, most ENTs agree on the importance of frequent follow-up visits during the first year of treatment (Q59 s.f.), and 64% of respondents agree on their timing during the first year (15 days, 1/3/6/9 months, and 1 year post-treatment initiation) (Q59 s.f.). After one year of biologic treatment, follow-ups are less frequent (every 6 months) (Q60 s.f.). We believe that frequent assessments, especially within the first 6 months, may be pivotal to evaluate response to treatment, detect adverse events (increased eosinophils), monitor adherence, and train patients to self-inject the medication [5]. On the other hand, after one year of treatment, the frequent visits (every 2 or 3 months) reported by a third of respondents (Q60 s.f.) may not be sustainable in the long term.

Notably, many ENTs do not evaluate CBCs at baseline to characterise inflammation and do not screen for increased eosinophils during the first months of biologic treatment. Evaluating eosinophils via CBC and total IgE prior to and during biologic treatment should be considered essential to the care of these patients. (Q61 s.f.) [15].

Since many ENTs do not consider lung function prior to and during biologic therapy (Q58, Q61, and Q62 s.f.), it is necessary to focus more on lung function assessments at those points in time. This is essential since response to treatment, as stated in EPOS2020 [25], is also defined by reductions in comorbidities such as asthma. ENTs that aim to work in multidisciplinary settings should perform questionnaire-based assessments of lung function to screen patients who require further testing, for example with the Asthma Control Test (ACT).

Practical management of patients with secondary CRSwNP (eosinophilic granulomatosis with polyangiitis, EGPA) and candidate for biologics (Q63-66 s.f.)

Our data (Q63 s.f.) suggest that in practice ENTs screen only selected patients with severe, uncontrolled CRSwNP for autoimmune parameters, and especially in case of known autoimmune disease (64%), increased eosinophils (49%), or concomitant eosinophilic disorders (58%). The blood tests used to exclude concomitant autoimmune diseases (Q64 s.f.) are reported in Figure 6 (Q64); the most cited are cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) or perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) (90%), and CBC with differential (73%). Regarding other exams used to screen patients suspected of rheumatologic diseases, most ENTs (95%) refer patients to a rheumatologist, and only 12% perform a preliminary nasal biopsy prior to referral (Q65 s.f.). There was no agreement about eosinophilia levels as thresholds considered suggestive of concomitant autoimmune disease in CRSwNP patients. Eosinophil levels > 1500/mcL are used by 32% of ENTs, followed by > 600/mcL by 20%. Interestingly, 17% stated they do not consider eosinophils to guide clinical decisions (Q66 s.f.).

EPOS2020 [25] suggests that EGPA should be ruled out in patients with severe CRSwNP not responding to conventional

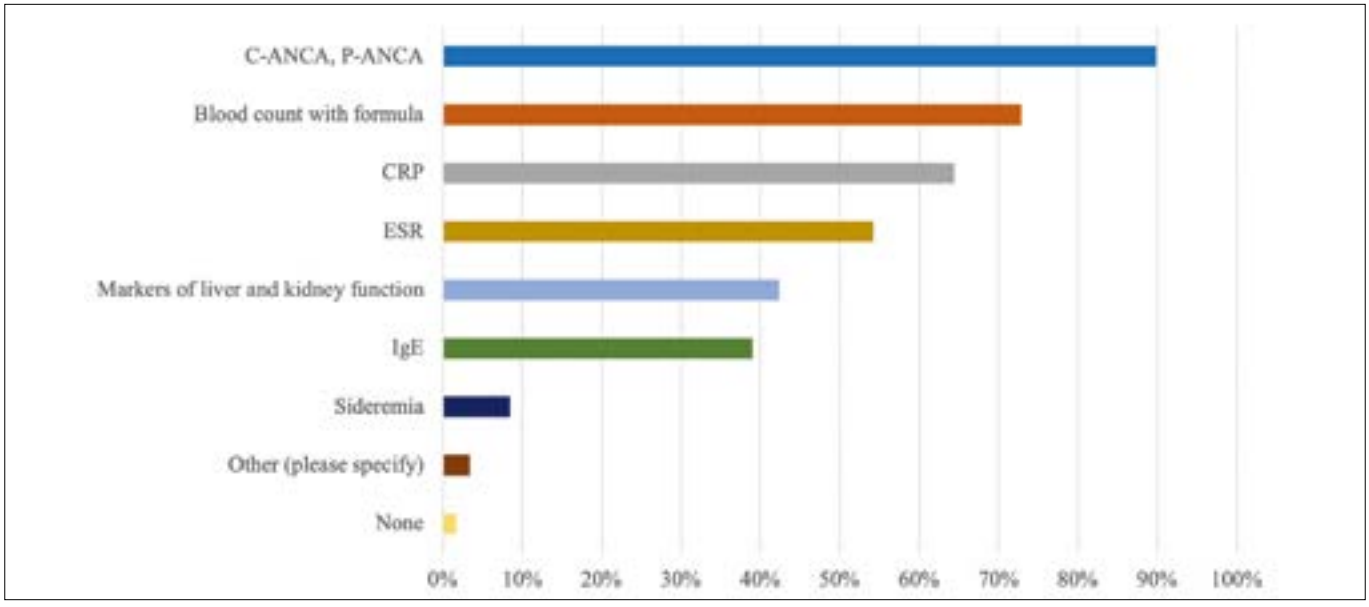

Figure 6. Blood chemistry tests considered useful for the exclusion of CRSwNP associated with autoimmune disease in the screening of a patient who is candidate for biological therapy (Q64 s.f.). C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibodies; P-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PNIF: Peak nasal inspiratory flow.

treatment, eosinophils over 1500/mcL, and Anti-neutrophil cytoplasmic antibody (ANCA) positivity as these should be considered active EGPA markers. Our data shows that this recommendation has not been incorporated universally by our survey respondents. The authors of this manuscript agree that CBC with differential, P-ANCA, and C-ANCA can be useful to exclude the presence of concomitant autoimmune diseases. These conditions should be always ruled out in candidates for biologic treatment with severe uncontrolled CRSwNP. This aspect becomes even more important considering that in some cases the administration of dupilumab may trigger the onset of EGPA in predisposed patients [52]. Finally, we would like to stress that EGPA may become apparent during or after the discontinuation of biologic treatments for asthma (with or without CRSwNP) [53-56].

Practical management of exacerbated respiratory disease (NSAID) (Q67-74 s.f.)

Our data suggest that ENTs are aware of NSAID-ERD, especially regarding its characteristic correlation with drugs and its typical clinical picture. The respondents consider that nasal endoscopy is an important diagnostic tool to diagnose NSAID-ERD (71%). However, for 81% documenting NSAID intolerance is crucial. Spirometry (69%) is also considered an important diagnostic tool (Q71 s.f.). ENTs consider bronchospasm (70%) and nasal obstruction (60%) pathognomonic signs for the diagnosis of NSAID-ERD (Q72 s.f.). In addition to the classic NSAID-ERD triad, respondents consider ocular symptoms (41%) or an itchy rash (39%) as characteristic symptoms (Q73 s.f.).

Most respondents (85%) are aware of the current definition of NSAID, NSAID-ERD that emphasises drug-induced exacerbation of respiratory symptoms in patients with asthma and nasal polyps (Q67-Q68 s.f.) [57]. Our survey shows that ENTs rely predominantly on symptom assessments to diagnose NSAID-ERD. Over half (51%) consider that in-depth anamnestic evaluation is useful to confirm diagnosis; however, most (90%) consider this insufficient and referral to an allergologist or a pulmonologist with additional allergy testing or bronchial reactivity studies is considered mandatory to definitively diagnose NSAID-ERD [58-60].

Concerning ENTs define NSAID-ERD disease control in terms of relapse of polyps (85%), asthma exacerbations (83%), symptom severity (83%), number of surgeries (61%), and eosinophil counts (56%, more often in serum than tissue) (Q74 s.f.).

Regarding acetylsalicylic acid (ASA) desensitisation as a therapeutic strategy for NSAID-ERD, almost half of the respondents (46%) reported that it is not performed in their centres. When it is practised it happens exclusively after standard medical therapy failure; indeed respondents believe that protocol of ASA desensitisation could be an option in patients that experienced OCS or surgical failure (Q69). Finally, there is a minority (12%) that believe that ASA desensitisation should never be proposed as a therapeutic option perhaps because it can be a high-risk procedure [61,62].

Conclusions

Our survey has shown that clinical practice in rhinology outpatient clinics has changed profoundly. ENTs working in rhinology centres have changed their activities, coinciding with the new therapeutic possibilities offered by targeted therapies. CRSwNP evaluations have become more complex because they involve diagnostic confirmation and determination of the immunologic profile (especially endotype). Evaluations of the endonasal situation in patients on biologics for asthma are also required. Finally, special attention must be paid during assessment of candidates for biologics by carefully evaluating past treatments and response to them, and the results of tests performed during multidisciplinary care. Counselling prior to the possible initiation of biologics is also particularly important. Patients have to be part of clinical decisions and have to be informed of the clinical course they will undergo.

The members of the Joint Committee on Biologics in Rhinology and of the Italian Rhinology Committee of the Italian Society of Otorhinolaryngology that discussed the results of the survey extrapolated practical recommendations for clinical practice in rhinology centres as summarised in Tables III and IV and approved by all the authors.

With this survey, we tried to emphasise the novelties present in rhinology clinics in terms of practical management and how closely ENTs adhere to and apply guidelines in clinical practice. We tried to underline how some aspects of the new diagnostic and therapeutic algorithm may be improved and provided practical suggestions. We believe that some of the practices and heterogenous behaviours reported by respondents may be conditioned by the novelty of the topic. It is worth noting that the conclusions drawn from this survey need to be considered also taking into account the limited number of respondents involved. In addition, some challenging topics will unquestionably be further debated. We need to discuss which tests to perform at baseline and which to repeat during follow-up and at what frequency. We also have to focus on the best timing of visits during follow-up. In an era of precision medicine, diagnostic protocols should align with the potential of targeted therapies such as monoclonal antibodies. Another challenge will arise when more biologics are approved for CRSwNP. Evidence from the literature and

Table II Comparison of EPOS guidelines to real-life practice regarding practical management of CRS.

	EPOS2020 guidelines	Italian real-life practice (% of responders)
Practical management of asthma patients with CRSwNP	A patient's self-assessment of their chest symptoms (wheeze, shortness of breath, chest tightness, and cough) and severity is often poor, or they may even be unaware that the lower respiratory tract is affected so objective assessment of lower airways is necessary	In the presence of a patient with moderately/severe CRSwNP who has never been operated on and has never taken biological therapy, 76% of respondents believe that evaluation of lower airways with objective testing is required
Practical management of severe CRSwNP patients naïve to surgical treatment	The EPOS2020 steering group was unclear as to whether nasal cytology, nasal lavage, blood eosinophilia and IgE in CRS patient at presentation of symptoms or after failure of previous treatment	In practice respondents consider in naïve patients with moderately/ severe CRSwNP blood eosinophil count (86.44%), Total IgE (79.66%), local nasal eosinophilia (52.54%).
	EPOS steering group suggested that QoL instruments are important for the management of CRS (100%) and the SNOT-22 was the most used 84%	In practice 98.31% of respondents believe that QOL Questionnaires are important and use SNOT-22
	Nasal endoscopy is an essential part of the rhinological examination	In practice, 100% of respondents believe that nasal endoscopy is important and use it
	EPOS criteria consider this scenario and put the endoscopic sinus surgery (ESS) procedure as a given in order to access biological therapy. However, EPOS also considers exceptional circumstances in which treatment can be accessed without prior ESS (e.g., not fit for surgery)	In real-life practice, the respondents usually take into consideration not only the contraindications to surgery but also factors predictive of failure and even categorical refusal of the patient
Practical management of CRSwNP patients initiating and during biologic therapy	Recommendations regarding the response criteria for biologicals in the treatment of CRS can be found that include reduced nasal polyp size, reduced need for systemic corticosteroids, improved quality of life, improved sense of smell and reduced impact of comorbidities	What parameters do you use to establish the response of biological therapy at 12 months? NPS (93%)
		SNOT-22(100%), NCS (32%), PNIF (18.64%)
		Improved comorbidities (ACT 28.81% – spirometry -16.95%) improved sense of smell, olfactometry 55.93%
	No practical management/timing guidelines are given	What is your timing of follow up for a patient with CRSwNP on biologic therapy in the first year of treatment?
		15 days, 1 month, 3 months, 6 months, 9 months, 1 year (64.41%)
		Every month (5.08%)
		Every 3 months (25.42%); every 6 months (5.08%)
Practical management of patients with secondary CRSwNP associated to EGPA	EGPA should be considered in any patient with severe nasal polyposis, not responding to conventional therapy, crusting/bleeding and severe symptoms, marked peripheral eosinophilia (usually > 1500/cells/ul or > 10%) and ANCA-positivity (not always present). However, Delphi consensus is unclear on if it essential to do an objective test for vasculitis in CRS after failure of previous treatment?	In practice, respondents consider it necessary to screen for autoimmunity patient with severe and uncontrolled CRSwNP in the case of very high values of blood hypereosinophilia (49.15%) without agreement on a specific cut-off, in case of other associated autoimmune diseases (64.41%). In case of obvious alterations of the nasal mucosa (e.g., septal perforations, crustiness) (35.59%)
Practical management of NSAID exacerbated respiratory disease	All patients with CRS should be asked about reactions to aspirin and NSAIDs. At least one documented reaction to aspirin or NSAIDs is required to make the diagnosis of N-ERD though history alone is not always reliable. Aspirin provocation tests are needed when the history is not clear	The diagnosis of NSAID-ERD is mainly based on clinical history including asthma, nasal polyps, and respiratory reactions to NSAIDs (85%)

Table III. Practical recommendations in diagnostic work up of CRSwNP.

Definition of type 2 inflammation in practice
CBCs and total IgE are useful blood biomarkers in defining type 2 inflammation in CRS patients
Definition of local eosinophilia may be useful, especially in cases with negative blood evidence of type 2 inflammation
Multidisciplinary evaluations that clearly define the presence of asthma or aspirin intolerance are useful in the definition of type 2 inflammation
It is highly recommended that treatment-naïve patients are accurately endotyped before initiating any treatment
Definition of severity of CRSwNP
Nasal endoscopy must be routinely performed to evaluate severity of disease
NPS and SNOT-22 scores are useful to define severity of disease
Lund-Mackay score applied to CT scan evaluation and endoscopic Lund-Kennedy endoscopic score (LKs) are useful to evaluate severity of disease
Evaluating completeness of previous intervention is recommended when assessing CT scans of patients who underwent previous surgery
Previous need of OCS must be carefully documented
Previous number and type of surgery performed for CRSwNP must be specifically investigated
Parameters for nasal obstruction should be taken into consideration in evaluating disease severity. (NCS and PNIF can be helpful)
Olfaction evaluation
It is recommended to routinely assess olfaction impairment in severe CRS patient by subjective and semi-objective tools
Olfaction impairment should be taken into account in order to define severity of disease
Evaluation of olfaction by specific olfactory test (Sniffin' sticks; Upsit) at time of diagnosis should be enhanced in Rhinology centres in which severe uncontrolled CRS patients are managed and biologics are prescribed
Multidisciplinary evaluation
In severe uncontrolled CRSwNP routinely request multidisciplinary assessments
In mild/moderate cases, multidisciplinary assessment is required if symptoms are suggestive of other comorbidities
Establish direct collaborative networks with asthma specialists (allergologist and pulmonologist) in order to facilitate the patient journey
Structured multidisciplinary boards may be useful in practice to discuss indications for a biologic in comorbid patients
Refer patients to immunologic evaluation in case of eosinophils > 1500/mcL and/or positive autoimmune tests
Pulmonary function should be assessed in all patients with severe CRSwNP, especially in candidates for a biologic (diagnose asthma, baseline definition of its severity and control)
Pulmonary function must be always performed in CRSwNP patients if pneumological symptoms are present

Table IV. Practical recommendations before starting with biologics and during treatment.

Recommendations before starting with biologics
All efforts should be made to define the presence of type 2 inflammation before starting with biologics (CBCs, total IgE, evidence of local eosinophilia etc)
A careful analysis of disease control must be performed, including response to previous medical and surgical treatment
CBCs must be performed before starting with biologics not only to define type 2 inflammation, but also to start with a baseline value that could be modified by biologics after
Cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) can be useful to exclude the presence of concomitant autoimmune disease in case of clinical suspicion
Measurement of olfaction with specific cut off (VAS olfaction Sniffin' stick Upsit) may be useful to start with a baseline value
Adequate counselling of patients is advised trying to involve them in the decision
Educating patients prior to treatment initiation regarding the possible therapeutic alternatives
Educating patients on possible adverse events and to provide quick referral if necessary
Provide logistic details and in hospital training for self-injection (caregiver involvement if patient is frail or needs support)
Plan the first injections in hospital and allow for observation time
Recommendations during treatment with biologics
Follow-up visits are highly recommended to monitor efficacy and adverse events (1 month, 3, 6 and 12 months) in the first year of treatment
After the first year of treatment, follow-up visits may be carried out every 6 months if there are no red flags (such as hypereosinophilia, etc.)
Follow-up visits should be standardised using specific assessment tools
Evaluation of olfaction by specific olfactory tests (Sniffin' sticks; Upsit) during biologic therapy to assess its efficacy is advised
Perform CBC at follow-up visits to screen variation of eosinophils. Timing should be chosen based on fluctuation of blood eosinophilia
Assess pulmonary function and asthma control in patients on biologics for CRSwNP and comorbid asthma during treatment

real-life data [41,63-65] will help reach better understanding of how to navigate the choice of biologic agent to maximise outcomes as much as possible from the perspective of personalised medicine.

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Author contributions
EDC: conceptualisation, resources and funding acquisition; EDC, CP, EC: methodology; SS: software; EDC, CP, GO, CC, DL, ST, SG, EC, VS, MT: formal analysis; EDC, CP, EC, GO, CC, DL, ST, SG, EC, VS, MT, SS: writing – original draft preparation; EDC, CP: writing – review and editing; FRMC, EP, IL, MG, GB, MDB, NL, AM, LM, GM, CV, AM, SM, VDE, AD, FA, VL, FA S, JG, DP, FP: critical revision.
All authors have read and agreed to the published version of the manuscript.

Ethical consideration
This study was promoted by Italian Commission of Rhinology and Italian Commission on the use of Biologics in Rhinology of the Italian Society of Otorhinolaryngology. The study was conducted as a quality improvement project with an educational purpose. Approval from the ethics committee is not accountable.

Data availability
The datasets generated during and/or analysed during the current questionnaire are available from the corresponding author on reasonable request.

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