Chronic rhinosinusitis with nasal polyps: how to identify eligible patients for biologics in clinical practice

Matteo Gelardi1, Corso Bocciolini2, Mario Notargiacomo3, Irene Schiavetti4, Cristiano Lingua5, Pietro Pecoraro6, Lucia Iannuzzi7, Vitaliano Antonio Quarantra8, Rossana Giancaspro1, Gianluca Ronca1, Michele Cassano1, Giorgio Ciprandi9

Italian Study Group on Nasal Polyps
1 Department of Otolaryngology, University of Foggia, Italy; 2 UOC of Otolaryngology Hospital Maggiore of Bologna, Italy; 3 Otorhinolaryngology Unit, Melzo Hospital, Milan, Italy; 4 Epidemiology, Biostatistics and Committe, Department of Direction, Istituto Giannina Gaslini, Genoa, Italy; 5 Otorhinolaryngology SC, ASO S, Croce and Carle, Cuneo, Italy; 6 ORL - Asp 6, Palermo, Italy; 7 ENT Clinic, Department of Biomedical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy; 8 Pneumology Unity, Di Venere Hospital, Bari, Italy; 9 Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy

SUMMARY
Objective. This study compared three severity measures for chronic rhinosinusitis with nasal polyps (CRSwNP). The outcome was to identify patients who are eligible for biological therapy.

Methods. 330 adult patients with CRSwNP were examined. Nasal polyp score (NPS), sinonasal outcome test (SNOT-22) and clinical-cytological grading (CCG) were compared. Clinical history, past surgery and asthma control test were also considered.

Results. Only 45 (13.6%) patients had a contextual positivity to the three severity measures. The concordance among tests was slight/fair. Patients with severe disease (all tests positive) had more impaired parameters. The mixed cytotype (OR = 4.07), nasal obstruction (OR = 10.06), post-nasal drip (OR = 1.98), embarrassment (OR = 2.53) and difficulty falling asleep (OR = 1.92) were significantly associated with severe CRSwNP.

Conclusions. To identify candidates for biological therapy, the contextual use of NPS, SNOT-22 and CCG is preferable. In this way, global assessment of CRSwNP, including morphology, inflammation, comorbidity, symptoms and quality of life is possible.

KEY WORDS: chronic rhinosinusitis with nasal polyps, nasal polyp score, SNOT-22, CCG, biological therapy
Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease characterised by different anatomic distributions, endotypes and phenotypes. In Western countries, type 2 immunity predominates, and consequently, abundant eosinophils infiltrate mucosal tissues. Persistent inflammation drives and maintains polyp formation and proliferation. In addition, patients with CRSwNP frequently have comorbidities, including asthma, allergy and aspirin hypersensitivity. From a clinical perspective, patients with CRSwNP experience bothersome symptoms that significantly affect the quality of life.

CRSwNP management includes medical treatments, mainly corticosteroids (CS). CS are usually prescribed topically (intranasal CS), but an oral CS course may be required to achieve adequate reduction of polyp size. However, medical treatment may be unsatisfactory; as a result, surgery represents an additional therapeutic option. Polyp surgery can be effective, but many patients, unfortunately, relapse and may require multiple operations.

The therapeutic scenario has changed after the launch of biologics, such as monoclonal antibodies antagonising pro-inflammatory mediators. In this regard, dupilumab is an anti-IL-4 monoclonal antibody that targets the alpha chain of IL-4Ra, a common receptor for IL-4 and IL-13. There is evidence that dupilumab is effective in patients with CRSwNP with and without asthma.

Recently, dupilumab has been approved in Italy by the Italian Agency for the Drugs (AIFA). Dupilumab prescription requires the compilation of an individual therapeutic plan by authorised specialists (hospital otorhinolaryngologists and allergists). The inclusion criteria for dupilumab eligibility include: i) adulthood; ii) documented diagnosis of severe CRSwNP; iii) severe CRSwNP defined by a nasal polyp score (NPS) ≥ 5 or a 22-item sinonasal outcome test (SNOT-22) score ≥ 50; and iv) failure of previous treatment. Regarding the latter requirement, two options are considered: i) at least two oral CS courses (in the past year) discontinued due to intolerance/adverse events or lack of efficacy; or ii) endoscopic sinus surgery followed by unsuccessful/inadequate response or complications.

These requirements may identify many eligible patients, but without pheno/endotyping them. NPS is an endoscopic score that assesses the polyp size and anatomy, but has not been completely validated. SNOT-22 mainly investigates symptom severity and quality of life (QoL) as perceived by the patient. Therefore, neither prognostic measure assesses inflammatory pattern or comorbidity. In this regard, a clinical-cytological grading (CCG) has been proposed to assess patients with CRSwNP. This tool allows obtaining useful clinical information that can also be collected over time. The GCC is also associated with the sense of smell impairment. In particular, CCG evaluates the presence of comorbidity, including asthma, allergy and aspirin hypersensitivity, and the pattern of the cellular infiltrate, including eosinophils, neutrophils and mast cells.

Based on this background, we tested the hypothesis that the contextual use of three tools, namely NPS, SNOT-22 and CCG, can be helpful to identify eligible candidates for biologic therapy. Therefore, the present nationwide study evaluated a large group of patients with CRSwNP in a clinical setting.

Materials and methods

Study population

This cross-sectional study enrolled patients who were consecutively visited in 23 Italian ENT Clinics. Inclusion criteria were: i) age ≥ 18 years; ii) male or female; iii) suffering from CRSwNP; and iv) informed written consent.

Exclusion criteria were: CRSsNP, severe anatomic defects of the nasal cavity and/or the nasal pyramid.

Study design

All patients were evaluated by: clinical history, objective examination, fibre-optic endoscopy, nasal cytology, skin prick test, and allergological and pulmonology visits. Diagnosis of CRSwNP was performed according to validated criteria according to European and International guidelines.

Outcomes

Outcomes of the current study evaluated concordance among prognostic tests and identified factors associated with positive contextual scores for severe CRSwNP, such as NPS ≥ 5, SNOT-22 ≥ 50 and CCG ≥ 7.

Nasal cytology includes sampling, processing and microscope reading. Sampling requires collecting cells from the surface of the middle portion of the inferior turbinate with a sterile disposable curette. The procedure was performed under anterior rhinoscopy, with an appropriate light source, and is painless. The sample obtained is immediately smeared on a glass slide, air-dried and stained with May-Grünwald-Giemsa (MGG) for 30 minutes. The stained sample was read by optical microscopy, with a 1,000x objective under oil immersion. Fifty fields were considered the minimum number to identify a sufficient number of cells. The count of each cell type was expressed by a semi-quantitative grading as previously described. Cytology also permits the detection of bacteria, spores and biofilm.
The skin prick test was performed as stated by the European Academy of Allergy and Clinical Immunology. The allergen panel consisted of the following: house-dust mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus), cats, dogs, grasses mix, Compositae mix, Parietaria judaica, birch, hazel trees, olive trees, cypress, Alternaria tenuis, Cladosporium and Aspergilli mix. The concentration of allergen extracts was 100 immune reactivity/mL (Stallergenes-Greer Italia, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as the positive control, and the glycerol-buffer diluent of the allergen preparations was used as the negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets. The skin reaction was recorded after 15 minutes by evaluating the skin response compared to the wheal given by the positive and the negative controls. A wheal diameter of at least 3 mm was considered as a positive reaction.

Nasal Polyp Score. Polyps were evaluated on each side through nasal endoscopy at each visit and graded based on polyp size, resulting in scores of 0 to 4. Zero is no polyp, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate, and 4 = large polyps causing complete obstruction of the inferior nasal cavity. The sum of the left and right nostril scores is the NPS. Values ≥ 5 define severe CRSwNP.

Sinonasal Outcome Test. SNOT-22 is a 22-items disease-specific, validated, patient-rated outcome measure. It is also considered the most suitable tool in terms of ease of use. It contains the key diagnostic symptoms included in the EPOS definition for CRS, as well as other items of importance to patients with CRS. It is increasingly used to measure the disease-specific quality of life in clinical practice routinely. Values ≥ 50 identify a severe score.

Clinical-Cytological Grading has been previously described in detail elsewhere. Briefly, CCG is a score based on both nasal cytology findings and comorbidities, including asthma, allergy and ASA hypersensitivity. For each variable, a score value was assigned: neutrophilic infiltrate was scored as 1, mast cell infiltrate was scored 1, eosinophilic infiltrate was scored 2 and eosinophilic + mast cell was scored 4; similarly, ASA hypersensitivity scored 1, asthma 2, allergy 2 and ASA sensitivity + asthma 3. CCG was composed as the sum of these individual scores. CCG global score is classified as low-grade (score 1-3), medium-grade (4-6) and high-grade (≥ 7).

Comorbidities. Asthma was diagnosed according to global initiative for asthma (GINA) guidelines. Allergy was diagnosed if the sensitised allergen caused symptoms after its exposure. Aspirin hypersensitivity was diagnosed according to international guidelines.

Asthma control test (ACT) questionnaire consisted of 5 questions with five possible responses, exploring the patient’s perception of his/her asthma control. The result ranged between 0 and 25, where 25 was the optimal asthma control and < 20 was poor asthma control.

Statistical analysis. No statistical sample size calculation was done a priori due to the exploratory nature of this study. Descriptive data were reported as mean with standard deviation, median with interquartile ranges, or count and percentage, as appropriate. Cohen’s kappa was used to assess the agreement between scores and has to be interpreted as follows: ≤ 0 no agreement; 0.01-0.20 none to slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; 0.81-1.00 almost perfect agreement (McHugh, 2012).

Univariable and multivariate stepwise logistic regression analyses were performed to evaluate all possible factors predicting a severe condition confirmed by all three scores (SNOT22; CCG and NPS). Variables with P < 0.20 in the univariate models were candidates for subsequent multivariate analysis. Results were expressed with odds ratio (OR) and related 95% confidence intervals (CI); two-sided p-values ≤ 0.05 were considered statistically significant.

The analyses were performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Three-hundred thirty patients (202 males, 128 females, mean age 52.1 years) participated in the study. Table I shows the stratification for the different severity scores: 99 (30%) patients were negative for all tests, 122 (37%) positive to one test, 64 (19.4%) to two and 45 (13.6%) to three. The concordance between tests was slight to fair, as reported in Table II. In particular, Cohen’s Kappa coefficient was 0.09 between NPS and SNOT-22, 0.28 between NPS and CCG, and 0.30 between SNOT-22 and CCG.

Patients with all three tests positive were defined as severe, and subdivided into two subgroups: not-severe and severe.

Table I. Severity from different scores.

| Severity confirmed: | N (%) |
|---------------------|-------|
| No score            | 99 (30.0) |
| One score           | 122 (37.0) |
| Two scores          | 64 (19.4) |
| All three scores    | 45 (13.6) |

Data are reported as count with percentage.
Table III reports the considered variables in all patients, not-severe and severe. There was a prevalence of males. Relapse after surgery was reported by 198 (60%) of patients. Using the criteria proposed by AIFA, 215 (65.2%) patients were candidates for dupilumab. Patients with severe CRSwNP had significant impairment of all considered variables, except for asthma control, dog allergy, aspirin hypersensitivity, presence of biofilm and bacteria. Multivariate analysis (Tab. IV) identified significant factors predicting severe CRSwNP. In particular, nasal obstruction (OR = 10.06), embarrassment (OR = 2.53), post-nasal drip (OR = 1.98) and trouble sleeping (OR = 1.92) were significantly associated with severe CRSwNP. Considering cytotypes: mixed type, mast cell and eosinophil, significantly predicted (OR = 4.07) severe CRSwNP.

Discussion

Chronic rhinosinusitis with nasal polyps is an inflammatory disease of the upper airways, commonly sustained by a type 2 inflammatory response. As a result, anti-inflammatory agents, topical or systemic, are the first-line strategy. However, this approach may be insufficient. Sinus surgery, therefore, is a treatment option in patients failing medical treatment. In addition, sinus surgery may be unsatisfactory as many patients have recurrent nasal polyps after surgery. Therefore, biological therapy may be an appropriate option in patients with refractory CRSwNP. The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) defined the indications for biological treatment, considering five aspects: reduced nasal polyp size, reduced need for systemic CS, improved QoL and sense of smell and reduced impact of comorbidities.

On the other hand, the AIFA established less stringent criteria for selecting eligible patients for dupilumab. In particular, the documentation of type of inflammation, olfactory dysfunction, and comorbidities were surprisingly not required. Consequently, the quote of eligible patients may become substantially high. These non-strict criteria might implicate an inappropriate prescription and potentially therapeutic failure. For these reasons, we designed a nationwide study conducted in a real-world setting. Most patients had underwent previous surgery, and 60% had recurrent polyps. Moreover, the findings showed that 30% of CRSwNP patients had no positive score for severe CRSwNP, but only 45 (13.6%) had reasonably severe disease, contextually confirmed by the NPS, SNOT-22 and CCG. Interestingly, the three tests were reasonably consistent. This aspect underlined the clinical relevance that they are not interchangeable and, consequently, it is convenient to consider them together. In fact, following AIFA criteria, two-thirds of these patients could be eligible for dupilumab, but only 13.6% should more appropriately receive the biologic using more discerning criteria. The direct consequence of this result could represent a higher probability of therapeutic success, prescriptive appropriateness, and lastly, saving of financial resources. Consistently, patients with severe CRSwNP, documented by multiple positive tests, had all parameters more impaired than other patients. In particular, multivariate analysis identified some factors associated with severe disease. Nasal obstruction is the key symptom able to predict a severe score. This symptom accurately reflects type 2 inflammation as confirmed in patients with allergic rhinitis. Another nasal symptom had a predictive role, such as post-nasal drip that depends on mucus discharge from the sinus. Hence, both symptoms are associated with congestion and hyperproduction of mucus: expression of upper airway inflammation. Embarrassment for symptoms and disturbed sleep affects the QoL and is a significant predictor of severe CRSwNP. These variables were derived from SNOT-22, whereas NPS did not generate any predictive outcome. Nasal cytotypes provided a relevant predictive factor, such as the mixed mast cell-eosinophil type. This result was consistent with a previous study that demonstrated that this cytotype is characterised by severe outcomes.

These results, therefore, seem to suggest that the combined use of three CRSwNP gradings could be a reasonable means to identify an eligible patient to dupilumab. On the
### Table III. Characteristics by all three severity scores.

| Characteristic                              | Total (n = 330) | Not severe (n = 285) | Severe (n = 45) | p*       |
|---------------------------------------------|----------------|----------------------|----------------|----------|
| Sex, males                                  |                |                      |                | 0.013*   |
| Age, years                                  | 52.1 ± 14.2    | 52.1 ± 14.54         | 52.1 ± 12.06   | 0.83     |
| Number of operations for nasal polyposis    | 1.2 ± 1.96     | 1.1 ± 2.05           | 1.6 ± 1.15     | 0.001*   |
| Relapse after surgery                       | 198 (60.0)     | 161 (56.5)           | 37 (82.2)      | < 0.001* |
| Eligibility for biologic                    | 215 (65.2)     | 170 (59.6)           | 45 (100.0)     | < 0.001* |
| Asthma                                      | 144 (43.6)     | 118 (41.4)           | 26 (57.8)      | 0.040*   |
| Asthma Control Test (ACT)                   |                |                      |                | < 0.001* |
| Partially controlled asthma                 | 53 (16.1)      | 42 (14.8)            | 11 (24.4)      |          |
| Not controlled asthma                       | 80 (24.3)      | 67 (23.6)            | 13 (28.9)      |          |
| Aspirin hypersensitivity                    | 62 (18.8)      | 52 (18.2)            | 10 (22.2)      | 0.53     |
| Aspirin hypersensitivity and asthma         | 47 (14.2)      | 37 (13.0)            | 10 (22.2)      | 0.10**   |
| Allergy diagnosis                           | 180 (54.5)     | 138 (48.4)           | 42 (93.3)      | < 0.001* |
| Dog allergy (SPT)                           | 34 (10.3)      | 28 (9.8)             | 6 (13.3)       | 0.47     |
| Cat allergy (SPT)                           | 36 (10.9)      | 27 (9.5)             | 9 (20.0)       | 0.035*   |
| Dust allergy (SPT)                          | 110 (33.3)     | 80 (28.1)            | 30 (66.7)      | < 0.001* |
| Inhalant sensitivity                        | 147 (44.5)     | 111 (38.9)           | 36 (80.0)      | < 0.001* |
| Eosinophilia + Mast cells                   | 130 (39.9)     | 97 (34.5)            | 33 (73.3)      | < 0.001* |
| Eosinophils                                 | 95 (29.1)      | 84 (29.9)            | 11 (24.4)      |          |
| Mast cells                                  | 76 (23.3)      | 75 (26.7)            | 1 (2.2)        |          |
| Neutrophils                                 | 25 (7.7)       | 25 (8.9)             | 0 (0.0)        |          |
| Biofilm                                     | 41 (12.4)      | 32 (11.2)            | 9 (20.0)       | 0.10**   |
| Bacteria (from 0 = absent to 4 = numerous)  | 0.0 (0.0-1.0)  | 0.0 (0.0-1.0)        | 0.0 (0.0-2.0)  | 0.06**   |
| Spores (from 0 = absent to 4 = numerous)    | 0.0 (0.0-0.0)  | 0.0 (0.0-0.0)        | 0.0 (0.0-0.0)  | < 0.001* |
| Need to blow the nose                       | 3.0 (2.0-4.0)  | 3.0 (2.0-4.0)        | 4.0 (4.0-5.0)  | < 0.001* |
| Sneezing                                    | 3.0 (2.0-4.0)  | 3.0 (2.0-3.0)        | 4.0 (3.0-4.0)  | < 0.001* |
| Rhinorhoea                                  | 3.0 (2.0-4.0)  | 3.0 (1.0-4.0)        | 4.0 (3.0-5.0)  | < 0.001* |
| Nasal obstruction                           | 4.0 (3.0-5.0)  | 4.0 (3.0-4.0)        | 5.0 (5.0-5.0)  | < 0.001* |
| Smell and taste dysfunction                 | 3.0 (2.0-4.0)  | 3.0 (2.0-4.0)        | 5.0 (4.0-5.0)  | < 0.001* |
| Postnasal drip                              | 2.0 (1.0-3.0)  | 2.0 (1.0-3.0)        | 3.0 (3.0-4.0)  | < 0.001* |
| Thick nasal discharge                       | 2.0 (1.0-3.0)  | 2.0 (0.0-3.0)        | 3.0 (3.0-4.0)  | < 0.001* |
| Cough                                       | 1.0 (0.0-2.0)  | 1.0 (0.0-2.0)        | 3.0 (2.0-3.0)  | < 0.001* |
| Ear fulness                                 | 0.0 (0.0-2.0)  | 0.0 (0.0-2.0)        | 2.0 (1.0-3.0)  | < 0.001* |
| Dizziness                                   | 0.0 (0.0-0.0)  | 0.0 (0.0-0.0)        | 0.0 (0.01.0)   | < 0.001* |
| Ear pain                                    | 0.0 (0.0-1.0)  | 0.0 (0.0-0.0)        | 1.0 (0.0-2.0)  | < 0.001* |
| Facial pain                                 | 1.0 (0.0-2.0)  | 0.0 (0.0-2.0)        | 2.0 (1.0-3.0)  | < 0.001* |
| Difficulty falling asleep                   | 2.0 (0.0-3.0)  | 1.0 (0.0-2.0)        | 3.0 (3.0-4.0)  | < 0.001* |
| Walking up at night                         | 0.0 (0.0-2.0)  | 0.0 (0.0-1.0)        | 2.0 (1.0-3.0)  | < 0.001* |
| Lack of a good night’s sleep                | 2.0 (0.0-3.0)  | 2.0 (0.0-3.0)        | 4.0 (3.0-4.0)  | < 0.001* |
| Waking up tired                             | 2.0 (0.0-3.0)  | 2.0 (0.0-3.0)        | 4.0 (2.0-4.0)  | < 0.001* |
| Fatigue                                     | 2.0 (0.0-3.0)  | 1.0 (0.0-3.0)        | 3.0 (3.0-4.0)  | < 0.001* |
| Reduced productivity                        | 1.0 (0.0-3.0)  | 1.0 (0.0-2.0)        | 3.0 (2.0-4.0)  | < 0.001* |
| Reduced concentration                       | 1.0 (0.0-3.0)  | 1.0 (0.0-2.0)        | 3.0 (2.0-4.0)  | < 0.001* |
| Frustration irritability                    | 2.0 (0.0-3.0)  | 1.0 (0.0-3.0)        | 3.0 (3.0-4.0)  | < 0.001* |
| Sadness                                     | 0.0 (0.0-2.0)  | 0.0 (0.0-2.0)        | 3.0 (2.0-4.0)  | < 0.001* |
| Embarrassment                               | 0.0 (0.0-3.0)  | 0.0 (0.0-2.0)        | 3.0 (2.0-4.0)  | < 0.001* |

Data are reported as count with percentage; mean with standard deviation; and median with interquartile range. *: p value is referred to univariate comparisons between groups: : p < 0.05; **: p < 0.20 (not significant, but included in the multivariate analysis).
contrary, to consider only one test, SNOT-22 or NPS, does not assure appropriate detection of a potential responder to biologic. Consistently, CCG concerns endotype and comorbidity, SNOT-22 assesses symptom severity and QoL and NPS anatomical aspects. Therefore, the combined use of these tests could be an operative proposal in daily practice. The strength of this study was the combined use of three different tests exploring the multifaceted pathogenesis of CRSwNP, its nationwide enrolment and the real-world setting. Thus, the results can mirror routine clinical practice. Moreover, CCG allows to identify type 2 inflammation by quantifying nasal eosinophils and mast cells, thus fulfilling the requirements of the EPOS document concerning the presence of type 2 inflammation for biologic eligibility. Consistently, severe CCG definitions includes the presence of type 2 biomarkers.

The limitations of this study include the absence of a sample size calculation, but the tested hypothesis did not require a specific number of patients, and also the lack of mediators and cytokine assessment, and its cross-sectional design. Moreover, a correct definition of patients suitable for biologics should include identification of responder subjects. However, the identification of responder cannot disregard the evaluation of treatment. In this regard, trials are ongoing to define precise cut-offs of type 2 biomarkers. It also should be noted that the nasal polyp score only describes the volume of the nasal polyp and omits some endoscopic findings such as secretions, mucosal oedema and altered healing, which potentially have a serious impact on the patient’s quality of life. Another limitation of this study was the lack of the direct evaluation of sinus and polyp inflammation. Nasal cytology could not completely reflect what happens in those tissues. However, the context of the current study was the comparison of three diagnostic tools in a real-life setting, such as clinical practice.

Therefore, this study underlines the conflicting results among tests concerning the proportion of patients who are eligible for biological therapy. The criteria proposed by the regulatory Agency were not selective as about two-thirds of patients could be eligible for dupilumab. Differently, the use of the three gradings considerably limited the proportion of candidates for biologic therapy.

### Conclusions

The present study showed that the combined use of SNOT-22, NPS, and CCG may be a reasonable option to identify patients who are eligible for dupilumab in clinical practice. Consistently, symptom severity, quality of life and endoscopic findings did not accurately evaluate CRSwNP severity, and comorbidity and inflammation should also be measured. Only complete and thorough assessment of CRSwNP patients allows appropriate prescription of biologics.

### Conflict of interest statement

The authors declare no conflict of interest.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Authors’ contributions

MG designed the study and discussed the manuscript, CB, MN, CL, PP, LI, RG, GR, MC collected the data and discussed the manuscript. IS and VAQ analysed the data. GC drafted the manuscript and revised the text.

### Ethical consideration

This study was approved by the Institutional Ethics of Foggia (approval number/protocol number 28-2020).
The Review Board approved the procedures used in this study and patients signed an informed consent. The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association’s Declaration of Helsinki.

Italian Study Group on Nasal Polyps: Luca Amorosa, Flavio Arnone, Paolo Luperto, Pasqua Irene Sciancalepore, Luigi Alonzi, Marilena Tomauulo, Alessandro Maselli Del Giudice, Anna Miglietta, Veronica Seccia, Giovanni Giulio Sulis, Cristiano Caruso, Valentina Rossi, Andrea Ciofalo, Consagra Calogera, Antonio Palma, Michela Mancini.

References

1 Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 2020;59(Suppl. 29):1-464. https://doi.org/10.4193/Rhin20.600
2 Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol 2016;6(Suppl. 1):S22-209. https://doi.org/10.1002/alr.21695
3 Ciprandi G, Gelardi M. Chronic rhinosinusitis with nasal polyposis: the role of personalized and integrated medicine. Monaldi Arch Chest Dis 2021:91. https://doi.org/10.4081/monaldi.2021.1769
4 Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. Laryngoscope 2017;127:550-555. https://doi.org/10.1002/lary.26391
5 DeConde AS, Mace JC, Levy JM, et al. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. Laryngoscope 2017;127:550-555. https://doi.org/10.1002/lary.26391
6 Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy 2019;4:2312-2319. https://doi.org/10.1111/all.13875
7 Hoy SM. Dupilumab: a review in chronic rhinosinusitis with nasal polyps. Drugs 2020;80:711-717. https://doi.org/10.1007/s40265-020-01298-9
8 https://www.aifa.gov.it/-/attivazione-web-e-pubblicazione-schede-di-monitoraggio-registro-dupixent. Accessed: May 2021.
9 Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013;131:110-116. https://doi.org/10.1016/j.jaci.2012.07.047
10 Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item sinonasal outcome test. Clin Otolaryngol 2009;34:447-454. https://doi.org/10.1111/j.1749-4486.2009.01995.x
11 Gelardi M, Iannuzzi L, De Giosa M, et al. Non-surgical management of chronic rhinosinusitis with nasal polyps based on clinical cytological grading: a precision medicine-based approach. Acta Otorhinolaryngol Ital 2017;37:38-45. https://doi.org/10.14639/0392-100X-1417
12 Gelardi M, Cassano M, Ciprandi G. The clinical relevance of the clinical cytological grading in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2020;146:462-463. https://doi.org/10.1016/j.jaci.2020.04.049
13 Gelardi M, Iannuzzi L, Quaranta N, et al. Olfactory dysfunction in patients with chronic rhinosinusitis with nasal polyps is associated with clinical-cytological grading severity. Acta Otorhinolaryngol Ital 2019;39:329-335. https://doi.org/10.14639/0392-100X-2426
14 Gelardi M, Iannuzzi L, Quaranta N, et al. Nasal cytology: practical aspects and clinical relevance. Clin Exp Allergy 2016;46:785-792. https://doi.org/10.1111/cea.12730
15 Bousquet J, Heinzerling L, Bachert C, et al.; Global Allergy and Asthma European Network. Practical guide to skin prick tests in allergy to aeroallergens. Allergy 2012;67:18-24. https://doi.org/10.1111/j.1398-9995.2011.02728.x
16 Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which is best? Clin Otolaryngol 2006;31:103-109. https://doi.org/10.1111/j.1749-4486.2006.01155.x
17 Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. Rhinology 2016;54:129-133. https://doi.org/10.4193/Rhin15.072
18 Global Initiative for Asthma. GINA guidelines. Global Strategy for Asthma Management and Prevention. 2021. https://www.ginasthma.org. Accessed: May 2021.
19 Licari A, Castagnoli R, Brambilla I, et al. Asthma endotyping and biomarkers in childhood asthma Pediatric Allergy Immunol Pulmonol 2018;31:44-55. https://doi.org/10.1089/ped.2018.0886
20 Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. Allergy 2011;66:818-829. https://doi.org/10.1111/j.1398-9995.2011.02557.x
21 Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey form assessing asthma control. J Allergy Clin Immunol 2004;113:59-65. https://doi.org/10.1016/j.jaci.2003.09.008
22 Hopkins C, Surda P, Bast F, et al. Prevention of chronic rhinosinusitis. Rhinology 2018;56:307-315. https://doi.org/10.4193/Rhin17.027
23 Ciprandi G, Cirillo I, Klersy C, et al. Nasal obstruction is the key symptom in hay fever patients. Otolaryngol Head Neck Surg 2005;133:429-435. https://doi.org/10.1016/j.otohns.2005.05.049

81