Practice parameter

The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis

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These evidence-based guidelines support patients, clinicians, and other stakeholders in decisions about the use of intranasal corticosteroids (INCS), biologics, and aspirin therapy after desensitization (ATAD) for the management of chronic rhinosinusitis with nasal polyposis (CRSwNP). It is important to note that the current evidence on surgery for CRSwNP was not assessed for this guideline nor were management options other than INCS, biologics, and ATAD. The Allergy-Immunology Joint Task Force on Practice Parameters formed a multidisciplinary guideline panel balanced to include the views of multiple stakeholders and to minimize potential biases. Systematic reviews for each management option informed the guideline. The guideline panel used the Grading of Recommendations Assessment, Development and Evaluation approach to inform and develop recommendations. The guideline panel reached consensus on the following statements: (1) In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation, low certainty of evidence). (2) In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation, moderate certainty of evidence). (3) In people with aspirin (nonsteroidal anti-inflammatory drug)-exacerbated respiratory disease, the guideline panel suggests ATAD rather than no ATAD (conditional recommendation, moderate certainty of evidence). The conditions for each recommendation are discussed in the guideline. (J Allergy Clin Immunol 2023;151:386-98.)

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Abbreviations used

AAAAI: American Academy of Allergy, Asthma & Immunology
ACAAI: American College of Allergy, Asthma, and Immunology
AERD: Aspirin (nonsteroidal anti-inflammatory)-exacerbated respiratory disease
ATAD: Aspirin therapy after desensitization
CI: Confidence interval
CRSwNP: Chronic rhinosinusitis with nasal polyposis
EGPA: Eosinophilic granulomatosis with polyangiitis
EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps
EtD: Evidence to decision
GI: Gastrointestinal
GIN: Guidelines International Network
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
ICAR-RS: International Consensus on Rhinology and Allergy: Rhinosinusitis
INCS: Intranasal corticosteroid
JTF-PP: Joint Task Force on Practice Parameters
MD: Mean difference
MID: Minimally important difference
NMA: Network meta-analysis
OR: Odds ratio
RCT: Randomized controlled trial
SNOT: SinoNasal Outcome Test
UPSIT: University of Pennsylvania Smell Identification Test

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory disease of the nasal mucosa and sinuses that lasts at least 12 weeks.[1] It affects about 2% to 4% of people with symptoms such as smell loss, nasal obstruction, thick nasal drainage, and facial pressure.[2] Some patients with CRSwNP also have comorbid asthma and develop acute respiratory reactions to nonsteroidal anti-inflammatory drugs. Patients with this clinical triad of conditions are classified as having aspirin (or nonsteroidal anti-inflammatory drug)-exacerbated respiratory disease (AERD).

CRSwNP is important because it negatively impacts quality of life. While there is no known cure for CRSwNP, there are many different management options. Although optimal patient outcomes require systematic summaries of all available evidence,[3] guidelines for the management of CRSwNP have historically not explicitly considered such summaries. Furthermore, several trials of interventions for CRSwNP were recently completed, calling for the need for updated clinical guidelines.[4-6]

These guidelines are based on updated and original systematic reviews of evidence conducted and reported separately.[7-9] The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN) and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations.[10] The recommendations, along with key remarks and conditions to consider when choosing treatments, are listed in Table I.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends"), or conditional ("the guideline panel suggests") and has the following interpretations.

Strong recommendation.

- For patients: Most fully informed people in this situation would want to follow the recommended course of action and only a small proportion would not.
- For clinicians: Most individuals should receive the intervention or test. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.

Conditional recommendation.

- For patients: The majority of fully informed people in this situation would want the suggested course of action, but many would not, and a discussion between them and their health care professional may help reach a decision (ie, shared decision making).
- For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. For each conditional recommendation we provide key conditions to guide working with patients in choosing their best treatment course.
- For policy makers: Policymaking will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on documentation of appropriate decision-making processes.

Values and preferences

Informed by a published survey of patients and clinicians, the guideline panel rated disease-specific quality of life and nasal symptoms as critical for decision making. Avoiding adverse effects from interventions is also considered important. The guideline panel, however, noted that there was possibly important uncertainty and variability in how much people value the critical outcomes.

Explanations and other considerations

Each recommendation is followed by remarks that further elaborate and contextualize the recommendation and important considerations to shape optimal shared decision making. The perspective of the guideline is that of the individual patient. These recommendations take into consideration cost, impact on health equity, acceptability by stakeholders, and feasibility of implementation. The Joint Task Force on Practice Parameters (JTF-PP) will create tools to facilitate the dissemination and implementation of the recommendations including oral presentations and an educational slide set. The consideration of aspirin therapy after

TABLE I. Summary of the recommendations

Question 1: Should INCS (topical corticosteroid), rather than no INCS, be used in CRSwNP?

Recommendation 1: In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation based on low certainty of evidence).

Remarks

Factors driving recommendation type:

- The small-to-moderate treatment effect and low certainty evidence when all of the different INCS delivery methods were considered together for the 2 critical outcomes, disease-specific quality of life and nasal obstruction symptoms, balanced by the low burdens of medications, drove the conditional recommendation.

Conditions that may be important during shared decision making:

- The NMA linked to this guideline showed that delivery method of INCS was potentially important. INCS stent, spray, and EDS are among the most beneficial of the INCS delivery methods across multiple patient-important outcomes.
- The costs, availability, accessibility, and practical implications of the different methods of INCS delivery are likely to influence patient decision making (see description of the interventions section).
- There is moderate certainty of evidence for the safety of INCS spray but safety may vary among the other delivery options. There is low or very low certainty in the safety of INCS using delivery methods other than spray.
- INCS have small treatment effect sizes. Patients with severe or rapidly recurrent disease may value more treatments with larger reductions in symptoms.
- There is probably uncertainty in the value and importance patients put on the outcomes that patients consider critical to decision making.

Question 2: Should biologics, rather than no biologics, be used CRSwNP?

Recommendation 2: In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation based on moderate certainty of evidence).

Remarks

Factors driving recommendation type:

- The varying values and preferences among different populations of individuals with CRSwNP drove the conditional recommendation.

Conditions that may be important during shared decision making:

- For patients who have a symptom for which the improvement was considered to be important while receiving treatments other than biologics (ie, INCS, surgery, or ATAD), not using biologics may be preferred.
- For patients using INCS for at least 4 weeks and who continue to have high disease burden, biologics may be preferred over other medical treatment choices.
- For patients who have higher disease severity at presentation, biologics may be preferred over other medical treatment choices.
- There is variability in efficacy among the biologics and this may influence the overall choice. Dupilumab and omalizumab are the most beneficial for most patient-important outcomes when comparing with other biologics based on results from the Oykhman et al[9] NMA linked to this guideline.
- Patients who value not having the burden of payment and insurance approvals may be less likely to choose biologics.
- Patients who want to avoid the inconvenience of trying potentially less effective medical therapies may prefer biologics.
- In AERD specifically, biologics may be preferred over ATAD for patients who have increased risk of harms associated with daily aspirin therapy, in patients who value the most efficacious therapies, and/or in patients who wish to avoid a strict daily oral medication regimen and its associated initial desensitization procedure.
- Patients with comorbid diseases that led to a dual indication for biologic treatment (eg, asthma) may be a reason to choose biologics in general and even specific biologics.

Question 3: Should ATAD, rather than no ATAD, be used in people with AERD?

Recommendation 3: In people with AERD, the guideline panel suggests ATAD rather than no ATAD (conditional recommendation based on moderate certainty of evidence).

Remarks

Factors driving recommendation type:

- The benefit of ATAD is moderate and is balanced by the risk of adverse effects that can lead to discontinuation.

Conditions that may be important during shared decision making:

- Risks that impact the safety of performing an aspirin desensitization such as severe poorly controlled asthma.
- Risks that impact safety of long-term aspirin use such as conditions or treatments that increase bleeding risk, such as age, male, low weight or BMI, hypertension, diabetes, smoking, prednisone use, or previous GI or intracranial bleed.
- Biologics may be preferred over ATAD in AERD for patients who have increased risk of harms with ATAD or in patients who value the most efficacious therapies and/or who are avoiding a strict daily oral medication regimen and its associated desensitization procedure.
- Patients intolerant to NSAIDs and who require an NSAID for alternative indications (eg. cardiovascular disease) may prefer ATAD over other options.

BMI, Body mass index; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

desensitization (ATAD) is only applicable for people who have AERD, whereas intranasal corticosteroids (INCS) and biologics apply more broadly to all persons with CRSwNP.

INTRODUCTION TO THE GUIDELINES

Aim of these guidelines and their specific objectives

The purpose of this document is to evaluate the current evidence and provide guidance on the use of INCS and biologics for CRSwNP and ATAD for AERD. It is important to note that the current evidence on surgery for CRSwNP was not assessed for this guideline nor were management options other than INCS, biologics, and ATAD. The primary target audience of these guidelines are specialists in allergy-immunology, otorhinolaryngologists, pulmonologists, general practitioners, and allied health practitioners. This document may also serve as the basis for development and implementation of locally adapted guidelines. By identifying gaps in the research literature, these guidelines

may help researchers direct attention to topics for which more studies are needed.

Description of the health problem

CRSwNP is an inflammatory disease of the sinonasal mucosa of at least 12 weeks' duration.[1] CRSwNP affects about 2% to 4% of adults.[2] The cardinal symptoms of CRSwNP are smell loss, nasal obstruction, thick nasal drainage, and facial pressure. Sinonasal symptoms adversely affect quality of life, including productivity, sleep, and exercise. People with CRSwNP often have comorbid asthma, an inflammatory condition of the lungs that causes reversible airflow obstruction and symptoms of shortness of breath, coughing, wheezing, and chest tightness. Severe asthma exacerbations cause emergency department visits, hospitalizations, and, rarely, death. Some mechanisms of inflammation, and therefore treatments, are common and shared between CRSwNP (upper airway inflammation) and asthma (lower airway inflammation).

There is no known cure for CRSwNP. There are, however, many different management options for CRSwNP. Previous clinical guidelines have narratively reviewed management options such as surgery (endoscopic sinus surgery), systemic corticosteroids, saline rinses, INCS, antibiotics, aspirin therapy following desensitization, and biologics.[4-6,11,12] The American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI) JTF-PP and CRSwNP work group members determined, through discussion, that the guideline would provide evidence-based guidance on 3 of these interventions: INCS, biologics, and ATAD. Several randomized controlled trials (RCTs) of these interventions for CRSwNP were recently completed, calling for the need for updated clinical guidelines specific to these interventions.[7-9]

Description of the target population

The target population for these recommendations is people with CRSwNP aged 18 years and older. Chronic rhinosinusitis without nasal polyposis is also an inflammatory disease of the nose and sinuses that lasts at least 12 weeks but differs from CRSwNP in that nasal polyps are not formed. CRSwNP is less common in people younger than 18 years old; however, recommendations for INCS and biologics may be appropriate for younger persons with CRSwNP or for conditions not considered in this guideline. CRSwNP can be subclassified further into diagnoses of AERD, allergic fungal rhinosinusitis, or eosinophilic granulomatosis with polyangiitis (EGPA), granulomatous polyangiitis, cystic fibrosis, or primary ciliary dyskinesia. Patients with cystic fibrosis, primary ciliary dyskinesia, and granulomatous polyangiitis were not considered in this clinical guideline. Patients with AERD are the focus of the third management question about ATAD but could also be considered for INCS or biologics. In contrast, patients who do not have AERD are not considered for ATAD but could be candidates for INCS or biologics. Studies in patients with allergic fungal rhinosinusitis and EGPA were included in the clinical guideline, though specific recommendations for patients who fit into these CRSwNP subtypes are not made in this clinical guideline. This clinical guideline is focused around 3 medical management questions: 1 specific to people with AERD, and the other 2 pertinent to all people who have CRSwNP.

Description of the interventions

INCS refer to multiple methods of delivering corticosteroids to the nasal and sinus mucosa. The different delivery modalities depend on the formulation of the drug and the device used to apply it. The types of delivery methods considered in this clinical guideline include nasal spray, rinse (also called flush or irrigation), exhalation delivery system, drops, and stents/dressing. Please see Table E1 in this article's Online Repository (available at www.jacionline.org) for details about these different delivery methods. Corticosteroid injections were not considered. INCS are self-administered by patients except when a stent or dressing is placed by a clinician with the proper expertise. All INCS delivery methods except for stent/dressing involve a patient using the medicine every day, sometimes more than once. Some delivery methods require manual dexterity and specific head positioning. INCS sprays are available without a prescription while most other forms of INCS require a prescription in the United States. Systemic corticosteroids such as oral tablets or intramuscular injections were not considered for this guideline.

Biologics are antibodies derived from organisms by recombinant technology. They are designed to target specific inflammatory pathways thought to be important in disease pathophysiology. Most patients who have CRSwNP have type 2 inflammation, and the biologics considered for people with CRSwNP are designed to modify the type 2inflammatory response. The biologics considered in the clinical guideline target IL-4 and IL-13 (dupilumab), IL-5 (benralizumab, mepolizumab, reslizumab), IgE (omalizumab), Siglec-8 (AK001), and IL-33 (etokimab). Dosing for biologics for CRSwNP varies based on the type of biologic and may be based on weight, laboratory tests, or severity of disease. Biologics require a prescription in the United States and parenteral administration.

ATAD is a 2-part process by which patients with AERD are first desensitized to aspirin and then, following desensitization, continued on daily aspirin therapy. During a desensitization, patients are gradually exposed to larger doses of aspirin ($\leq$325 mg) over a period of 1 to 3 days depending on which protocol is used. By definition, patients with AERD frequently develop upper and/or lower respiratory reactions at some point during the desensitization. However, patients who recently underwent sinonasal surgery or who are taking certain other medications may report few to no symptoms during the process. Following the desensitization, patients are then instructed to take aspirin daily. While there is no global consensus as to the specific dose of aspirin needed for treatment of AERD, the available RCTs most commonly used doses between 650 mg and 1300 mg per day. Importantly, aspirin must be taken every day after a desensitization. If a patient misses a dose for >2 days, they must be evaluated by their allergist prior to continuing aspirin therapy and they may have to redo the desensitization procedure. Finally, it should be stressed that the desensitization itself does not provide clinical benefit for patients with AERD but instead the means by which patients with AERD are able to take aspirin daily.

Description of the outcomes

Disease-specific quality of life in the trials was measured using different types of standardized and validated questionnaires. The most commonly used tools were the SinoNasal Outcome Test (SNOT) which is a 20-item (SNOT-20) or 22-item (SNOT-22) patient self-administered questionnaire.[13] The SNOT-22 scale is from 0 to 110 (total score), with higher scores associated with a worsening impact on disease-specific quality of life. In this guideline, scales other than SNOT-22 were normalized to the SNOT-22 scale using accepted techniques.[14] The SNOT-22 has a minimally important difference (MID) of 8.9 to 12 points improvement (which would result in a lower score using the total score); the CRSwNP work group selected 8.9 as the *a priori* MID.[15,16] This means that a patient whose SNOT-22 score increased more than 9 to 12 points is likely to have a patient-important worsened disease-specific quality of life and that, conversely, a decrease in 9 to 12 points means a patient is likely to have a patient-important improvement in disease-specific quality of life. Nasal symptom scores were patient-reported and could be total nasal symptom scores or nasal obstruction specifically. Multiple scales (eg, 0-3, 0-10, 0-100) were encountered in the trial literature, and for each outcome, the measurement was adjusted to the most commonly used scale for that specific intervention. Because there is no MID reported for nasal symptom scores, the CRSwNP work group, with input from patient participants, set an MID of 0.3 for the 0 to 3 scale and 1.0 for the 0 to 10 scale. Sense of smell was defined both as patient-reported (with various scales, 0-3 being most common) and as objectively measured, with the University of Pennsylvania Smell Identification Test (UPSIT) being the most common test.[17] Following a discussion within the CRSwNP work group that noted that subjective and objective estimates were consistent, a decision was made to normalize all smell-related outcomes to the UPSIT. The UPSIT is on a scale of 0 to 40, where a higher score translates to a better smell function. Because there is not an MID reported for the UPSIT, the CRSwNP work group, with input from patient participants, set an MID of 4.0 for the 0 to 40 scale. MID thresholds were established or agreed on by the CRSwNP workgroup for the following outcomes for which established MIDs were not available: rescue surgery (5% risk difference); any adverse event (5% risk difference); serious adverse events (1% risk difference); nasal polyp score (0.3 on 0-3 scale or 1.0 on 0-8 scale); nasal endoscopy score (3 on 0-12 modified Lund-Kennedy scale)[18]; and computed tomography imaging (4 on 0-24 Lund-Mackay imaging scale).[19]

METHODS

Organization, panel composition, planning, and coordination

There were 4 groups who supported the development of this guideline. First, the JTF-PP provided overall oversight of the guideline development with support from their parent organizations, the ACAAI and the AAAAI. Second, a CRSwNP work group consisting of allergy-immunology specialists, otorhinolaryngologists, and methodologists started with Population, Intervention, Comparison, and Outcomes questions; rated the importance of outcomes *a priori*; assessed prior systematic review and meta-analyses; performed up-to-date searches and systematic review/meta-analyses as needed; led the writing of technical reports; and organized materials in preparation for the guideline panel meeting. Some of the CRSwNP work group members were also JTF-PP members. Third, the guideline panel included members of the CRSwNP work group, 4 patient participants, and 4 researchers with experience in evidence synthesis and guideline development. The 4 patient participants were identified by members of the work group. The guideline panel reviewed information from the work group and formed recommendations and an evidence-to-decision (EtD) framework. Fourth, the Evidence in Allergy group at McMaster University supported the evidence synthesis process and its linkage to decision making. The primary responsibility of the guideline panel was to participate in a virtual meeting where the guideline recommendations were discussed. See Table E2 for a list of the members in each group.

The guideline panel developed the recommendations and appraised the certainty of the supporting evidence following the GRADE approach. The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by the policies and procedures derived from the GIN-McMaster Guideline Development Checklist (https://cebgrade.mcmaster.ca/guidecheck.html) and intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.

Project oversight was provided by a clinical chair (A.T.P.) and assisted by 2 guideline methodology cochairs (D.K.C. and M.A.R.). The clinical chair (A.T.P.) vetted and appointed individuals to the guideline panel. The methodology cochairs (D.K.C. and M.A.R.) vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline-development process, including use of the GRADE approach.

The panel's work was done using Web-based tools: Google Forms (docs.google.com/forms/); GRADEpro Guideline Development Tool (www.gradepro.org); and multiple video-based meetings including a meeting where the entire panel discussed and finalized the recommendations.

Guideline funding and the management of competing interests

Development of these guidelines was funded by the JTF-PP, which is financially supported by the ACAAI and AAAAI. Leadership from the ACAAI and AAAAI reviewed and approved the research questions after input from the JTF-PP and the CRSwNP work group. Members of the JTF-PP, CRSwNP work group, and guideline panel received no payments for their work related to this guideline. The JTF-PP funded the technical reports used to support the clinical guideline process.

The disclosure of secondary interests and the management of potential conflicts for all participants was conducted in accordance with JTF-PP policies, which are posted on its website (www.allergyparameters.org). At the time of appointment, ≥50% of the guideline panel had no conflicts of interest as defined by the JTF-PP policy and judged by the clinical chair (A.T.P.).

Before appointment to the panel, all JTF-PP, CRSwNP, and guideline panel members completed the JTF-PP declaration of interest forms except for the 4 patient participants whose potential conflicts of interest were reviewed separately by the clinical chair (A.T.P.). None of the patient participants was found to have a potential conflict of interest. Team members who were judged to have a real, potential, or perceived conflict of interest related to the content in a research question were excused from voting on the final recommendation or on judgments related to items in the EtD tables.

Selection of questions and outcomes of interest

Members of the JTF-PP and CRSwNP work group worked collaboratively to consider potential questions to be addressed in these guidelines. Using group discussion, consensus was achieved to address 3 questions. The selected interventions and questions represent the top-prioritized issues identified by the group:

- Question 1: Should INCS (topical corticosteroid), rather than no INCS, be used in CRSwNP?
- Question 2: Should biologics, rather than no biologics, be used in CRSwNP?
- Question 3: Should ATAD, rather than no aspirin, be used in people with AERD?

The panel selected outcomes of interest for each question *a priori*. In brief, the panel brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach. The panel

considered the patient perspective by reviewing literature about the outcomes in CRSwNP; a subsequent article examining patient perspective that was not available during the initial outcome rating had similar findings.[20-22] After a list of outcomes was created, each CRSwNP work group member independently scored each outcome on a scale of 1 to 9 (from least important to critical). Next, discussion among the CRSwNP work group led to consensus selection of 2 critical outcomes: disease-specific quality of life and nasal obstruction symptom score. Several important outcomes were also identified: adverse events; sense of smell; use of rescue surgery; use of systemic corticosteroids; nasal polyp score; sinus imaging severity; and nasal endoscopy scores.

Evidence review and development of recommendations

For each guideline question, the evidence synthesis team prepared an evidence profile and a GRADE EtD table using the GRADEpro software. Each EtD table summarizes the results of a systematic review of the literature that was either updated or performed *de novo* for these guidelines. For question 1, a *de novo* systematic review and network meta-analysis (NMA) was performed.[8] NMA simultaneously compared multiple competing treatment options to allow inferences on comparative efficacy and safety. For question 2, a *de novo* systematic review and NMA was performed.[9] For question 3, an existing systematic review and meta-analysis was updated (through September 1, 2021).[7,9] The EtD tables include the information about the effects of interventions on health outcomes, the values and preferences (ie, relative importance of outcomes), resource utilization (cost-effectiveness), health equity issues, acceptability of interventions to stakeholders, and the feasibility of implementation. The guideline panel reviewed the draft EtD tables before and during the guideline panel meeting making suggestions for corrections and clarifications. To ensure that recent studies were not missed, searches were updated up to September 1, 2021, and panel members were asked to suggest any additional studies that they may have known about and that fulfilled the inclusion criteria for the systematic reviews.

Under the direction of methodologists, the evidence synthesis team followed the general methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* for conducting updated or new systematic reviews of intervention effects.[14] The certainty in the body of evidence about the health effects (also known as quality of the evidence or confidence in the estimated effects) was assessed for each outcome of interest following the GRADE approach based on the following domains: risk of bias; imprecision; inconsistency and publication bias; presence of large effects; dose-effect relationship; and an assessment of the effect of plausible residual and opposing confounding. They also considered GRADE guidance specific to NMA (eg. network imprecision).[23] The certainty was categorized into 4 levels: very low; low; moderate; or high.

During a guideline panel meeting held via video conferencing, followed by additional online communication, the panel developed recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a patient perspective and came to consensus on the following: the certainty in the evidence; the balance of benefits and harms of the compared management options; and the inferences about the values and preferences associated with the decision. The guideline panel also explicitly considered resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength) and remarks. In this guideline, all 3 guideline recommendations reached consensus. All members of the panel reviewed and approved the final guidelines.

Interpretation of strong and conditional recommendations

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. Table II provides the interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Document review

Draft guidelines were reviewed by all guideline panel members, CRSwNP work group members and JTF-PP members and were revised based on feedback. Next, the guidelines were posted for public comment and revised based on feedback. Finally, the guidelines were reviewed by experts appointed by the ACAAI and AAAAI. The guideline will undergo journal peer review. All reviewers' comments will be addressed, and changes will be made after discussion among the guideline panel, CRSwNP work group, and the JTF-PP.

How to use these guidelines

This JTF-PP guideline is primarily intended to help clinicians make treatment decisions. They may also be used by patients. Other purposes are to inform policy, education, and advocacy, and to clarify future research needs.

These guidelines are not intended to serve or to be viewed as a standard of care. Decision makers should not treat the recommendations in these guidelines as binding mandates. No recommendation can fully consider all circumstances that might affect the potential benefits, harms, and burdens of an intervention in individual patients or in a given clinical setting. Clinicians must make decisions based on the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen management option. Clinicians' and patients' decisions may also be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, and availability of treatments. Thus, no one charged with overseeing or evaluating the actions of clinicians should apply the recommendations blindly.

These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. The JTF-PP does not warrant or guarantee any products described in these guidelines.

Translation and quoting

When quoting or translating recommendations from these guidelines, any qualifying remarks that accompany each recommendation should not be omitted (including statements regarding special circumstances and assumed values and preferences). These statements are integral to the recommendations and serve to facilitate more accurate interpretation.

RESULTS

Question 1: Should INCS (topical corticosteroid), rather than no INCS, be used in CRSwNP?

Summary of the evidence, benefits, and harms. Summary of findings and the EtD tables for this question are posted in Table E3 in this article's Online Repository (available at www.jacionline.org; see also Fig 1). For this question the *de novo* systematic review was updated up to September 1, 2021.[8] For disease-specific quality of life using the SNOT-22 scale where a difference of ≥8.9 points is considered important to patients, the mean difference (MD) compared to placebo of intervention with INCS rinse (MD: −6.83; 95% confidence interval [CI]: −11.94, −1.71) and exhalation delivery system (MD: −7.96; 95% CI: −14.64, −1.08) were among the most beneficial.[8] It is important to note that these changes in SNOT-22 score (eg, −6.83 and −7.96) represent the differences from baseline to end of study that exceed the changes in the comparison arm of the trial (ie, between-group difference). For nasal obstruction symptoms score, where >0.3 points on a 0 to 3 symptom scale is considered patient-important, interventions with stent (MD: −0.31; 95% CI: −0.54, −0.08), spray (MD: −0.51; 95% CI: −0.61, −0.41), and exhalation delivery system (MD: −0.35;

TABLE II. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most fully informed people in this situation would want the recommended course of action and only a small proportion would not.	The majority of fully informed people in this situation would want the suggested course of action, but many would not, and it may need more discussion between them and their health care professional first.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with that patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence; in such instances, further research may provide important information that may alter that recommendation.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

95% CI: −0.51, −0.18) were among the most beneficial.[8] Discussion among the guideline panel centered around small versus moderate for judgment of desirable effects, given that both point estimates were very near to the MID. Consensus was that small-to-moderate desirable effects are noted with INCS.

There were no differences found in rates of adverse events, serious adverse events, adverse events requiring a clinical intervention, or adverse events associated with discontinuation of the study for any comparison. There is low or very low certainty in the safety of INCS using delivery methods other than spray. Rates of serious adverse events were 1.6% in the placebo group and ranged from 1.3% to 0.8% in the intervention group depending on the delivery method.[7] Specific adverse events (eg, epistaxis) and cortisol axis suppression were not consistently reported, and adverse effects requiring long-term exposure such as osteoporosis were not assessed. The type of topical corticosteroid, dose, and the possibility that patients are taking additional forms of topical corticosteroid, such as inhalers and skin creams in addition to the INCS, led the group to conclude that undesirable effects may vary in patients.

Assumed values and preferences. Panel members agreed that there is probably uncertainty in the value and importance patients put on the outcomes of disease-specific quality of life and nasal symptoms scores. The panel members noted a report from Hopkins et al[20] detailing results from an online survey with 235 people with CRS (155 practitioners who have patients with CRS and 80 patients with CRS). Symptom-based outcomes were suggested by both practitioners and patients to be the most important. The JTF-PP guideline patient partners indicated that other outcomes such as sense of smell and quality of sleep may be the most important outcomes for some people.

For detailed consideration of values and preferences, acceptability of interventions, feasibility of implementation, and required resources please see the EtD table (Table E3).

Balance between desirable and undesirable health effects. Panel members thought that the overall balance of effects favored INCS. However, they acknowledged that using INCS depends on values and preferences of patients and/or their caregivers for individual outcomes. For those who value the improvement in disease-specific quality of life and nasal symptoms more than the small and varying risk of adverse effects, the balance may favor INCS use. Other management options for CRSwNP that patients and their caregivers could consider include saline rinse, surgery, biologics, and antibiotics.

Recommendation. In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation based on low certainty of evidence).

Remarks. The conditional recommendation for INCS was driven by the small-to-moderate treatment effect size across the 2 critical outcomes, low certainty evidence (particularly in quality of life and harms), and uncertain but anticipated variability in patient values and preferences. Only INCS spray has an effect size whose estimate and 95% CI does not cross the MID achieved for nasal obstruction symptoms: −0.51 (95% CI: −0.61, −0.41) with MID of 0.3.

There are many conditions that may be important during shared decision making for using INCS for CRSwNP. The delivery method of INCS is potentially important. INCS stent, spray, and exhalation delivery system are among the most beneficial of the INCS delivery methods across multiple patient-important outcomes (symptoms, smell, need for rescue surgery). The costs and availability of the different methods of INCS delivery are relevant. Prespecified subgroups, such as studies where surgery occurred at the beginning of the study, did not alter the overall treatment effect. There is moderate certainty of evidence in the safety of INCS spray, but undesirable effects may vary among different INCS treatment types.

Implementation considerations. In all cases the diagnosis of CRSwNP must be confirmed by using appropriate diagnostic tools including direct visualization of nasal polyps.[11,12] Not all delivery methods are feasible for every patient. The access to some of the delivery methods may be limited by cost, insurance coverage, and availability of clinical expertise necessary to apply certain delivery methods (eg, stents).

Implications for further research. When reviewing the evidence and considering all other factors influencing this recommendation, the guideline panel identified the following 3 priorities for further research:

1. More direct comparison RCTs of INCS treatments and comparison with other management options. Large, collaborative, multicenter RCTs using conservative sample size calculations informed by the meta-analyses linked to this guideline will more likely lead to definitive results rather than the current situation—multiple small, often inconclusive, RCTs.
2. Robust research on which outcomes are important to patients and the most credible MIDs for these outcomes.
3. See the linked meta-analysis that outlines other research priorities.[8]

Question 2: Should biologics, rather than no biologics, be used in CRSwNP?

Summary of the evidence, benefits, and harms. Summary of findings and the EtD table (Table E4 in this article's Online Repository at www.jacionline.org) for this question are posted in the Online Repository (see also Fig 2). For this question the *de novo* systematic review was updated up to August 4, 2021.[9] For the MD in disease-specific quality of life using the SNOT-22 scale where a difference of ≥8.9 points is considered patient-important, dupilumab (MD: −19.91; 95% CI: −22.50, −17.32) and omalizumab (MD: −16.09; 95% CI: −19.88, −12.30) were the most beneficial.[9] For nasal symptoms scores, where 1 point is the MID on a 0- to 10-point symptom, dupilumab (MD: −3.25; 95% CI: −4.31, −2.18), omalizumab (MD: −2.09; 95% CI: −3.15, −1.03), and mepolizumab (MD: −1.82; 95% CI: −3.13, −0.50) were the most beneficial.[9] None of the biologics had a significantly different adverse event rate than placebo; however, the certainty of evidence was low or very low.[9] Data from use of biologics for other conditions suggest some infrequent risks, such as anaphylaxis with omalizumab (0.09% for people with asthma)[24] and conjunctivitis with dupilumab (2% for patients with CRSwNP).[25]

Assumed values and preferences. Similarly to questions 1 and 3, panel members agreed that there is probably uncertainty in the value and importance patients put on the critical outcomes of disease-specific quality of life and nasal symptoms scores. For detailed consideration of values and preferences, acceptability of interventions, feasibility of implementation, and required resources please see Table E4, the EtD table .

Balance between desirable and undesirable health effects. Panel members thought that the overall balance of effects favored biologics over no biologics. However, they acknowledged that using biologics depends on the values and preferences of patients and/or their caregivers for individual outcomes. For those who value the improvement in disease-specific quality of life and nasal symptoms more than the small and varying risk of adverse effects, the balance may favor biologic use. Other management options for CRSwNP that patients and their caregivers could consider include saline rinse, surgery, INCS, antibiotics, and, for people with AERD, ATAD.

Recommendation. In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation based on moderate certainty of evidence).

Remarks. The factor driving the conditional recommendation is the availability of other options that should be considered or used together with biologics such as INCS, surgery, and in patients with AERD, ATAD. There are several conditions that may be important during shared decision making about biologics for CRSwNP. Patients who have not sufficiently benefitted from treatments other than biologics, such as any combination of INCS, surgery, or ATAD, may be more likely to value the higher certainty and magnitude of benefits that dupilumab, omalizumab, or mepolizumab are likely to provide. Not all patients, however, need to try medical therapies that are likely to deliver little to no patient-important benefits, or whose efficacy or safety are uncertain. For example, the panel inferred those patients with high baseline disease severity, would likely value the higher certainty and magnitude of benefits over the lower certainty for modest benefits delivered by other medical therapies (eg. INCS [see recommendation 1], ATAD, antibiotics) and harms (eg. ATAD). Conversely, patients with low disease burden, regardless of nasal polyp size, and who have not tried other therapies, might prefer to avoid the burden of systemic therapy with a biologic and its associated payment and insurance negotiation, and accept the lower certainty for modest benefits and less-invasive nature of INCS.

The linked systematic review and NMA showed that the biologics vary in their magnitude of benefits and harms and certainty of evidence across outcomes.[9] Dupilumab and omalizumab are the most beneficial for the most patient important outcomes when comparing with other biologics, followed by mepolizumab.[9] Patients with comorbid diseases and dual indications for a specific biologic may help direct clinicians to choose a specific biologic (eg, dupilumab improves both atopic dermatitis and CRSwNP; dupilumab's increase in peripheral eosinophilia and possible unmasking of EGPA[26-29] may not be optimal for patients with EGPA and mepolizumab or benralizumab might be preferred instead). Biologics may be preferred over ATAD in AERD, especially for patients who have increased risk of harm with ATAD (history of gastrointestinal [GI] bleeding, prednisone use, hypertension, diabetes, smoking, male sex, and lower weight or body mass index).

Implementation considerations. As with all interventions for CRSwNP, the diagnosis of CRSwNP must be confirmed. Some patients may not be able to access biologic therapy due to costs or other barriers to access and some patients may be able to access some biologics but not others. Some people with biologics may receive them in health care settings and others may self-administer in their home.

Implications for further research. When reviewing the evidence and considering all other factors influencing this recommendation, the guideline panel identified the following priorities for further research:

1. More direct comparison RCTs of active treatments and studies of combination of therapies (ATAD and biologics treatment).
2. As described for the INCS recommendations, robust research addressing which outcomes are important to patients and the most credible minimally important differences for these outcomes.
3. Better tools to predict and quantify treatment response before starting biologics.

	Patient-Important outcomes								Surrogate Outcomes		
	Critical Outcomes		Important Outcomes								
	HR-QoL SNOT-22 (0-120)	Symptoms (Nasal Obstruction) VAS (0-3)	Smell UPSIT (0-40)	Rescue Surgery	Severe Adverse Events	Any Adverse Events	AE intervention	AE discontinuation	Polyp Size (0-3)	Endoscopy Lund-Kennedy (0-12)	Imaging Lund Mackay (0-24)
Placebo (reference)	-19.41	-0.56	3.54	13.58%	2.76%	28.66%	0.66%	1.73%	-0.60	-3.63	-2.27
Stent	2.35 (-5.92, 10.62)	-0.31 (-0.54, -0.08)	3.81 (1.22, 6.39)	-10.3% (-12.9%, -0.2%)	-1.3% (-5.6%, 2.9%)	-4.2% (-15.5%, 7.0%)	-0.2% (-3.5%, 3.2%)	-1.5% (-5.8%, 2.7%)	-0.53 (-1.11, 0.04)	-1.85 (-5.62, 1.92)	-0.82 (-5.05, 3.41)
Spray	-3.62 (-9.27, 2.04)	-0.51 (-0.61, -0.41)	3.24 (2.05, 4.42)	-10.7% (-13%, -2.1%)	-0.1% (-0.8%, 0.5%)	2.7% (-0.7%, 6.1%)	-0.4% (-1.0%, 0.3%)	-0.6% (-1.3%, 0.0%)	-0.64 (-0.85, -0.43)	-0.84 (-3.30, 1.63)	0.38 (-2.01, 2.78)
Rinse	-6.83 (-11.94, -1.71)	-0.21 (-0.76, 0.33)	2.77 (-0.84, 6.39)		0.00% (-4.3%, 4.2%)	-0.6% (-8.5%, 7.3%)	-0.6% (-5.1%, 3.8%)	-0.1% (-4.4%, 4.1%)	-0.46 (-1.31, 0.39)	-0.64 (-3.24, 1.97)	0.93 (-2.17, 4.04)
EDS	-7.86 (-14.64, -1.08)	-0.35 (-0.51, -0.18)	4.10 (1.69, 6.52)	-4.3% (-6.9%, -0.9%)	-1.0% (-3.3%, 1.3%)	2.9% (-14.8%, 20.7%)	-0.3% (-2.0%, 1.3%)	-0.9% (-3.4%, 1.7%)	-0.56 (-0.97, -0.14)		
Drops		-0.15 (-0.61, 0.31)	5.03 (1.88, 8.18)	-11.0% (-13.6%, 42.3%)	0.8% (-2.1%, 3.8%)	3.1% (-6.7%, 13.0%)	-0.5% (-3.3%, 2.3%)	-0.9% (-3.9%, 2.2%)	-1.17 (-2.36, 0.02)		-1.02 (-4.80, 2.76)
Nebulizer					-0.1% (-12.2%, 11.9%)	2.7% (-12.1%, 17.5%)	-0.4% (-12.4%, 11.7%)	-0.6% (-12.7%, 11.5%)		-0.96 (-6.57, 4.66)	-0.29 (-4.24, 3.67)
Injection									-0.11 (-0.99, 0.77)		
High Dose Spray	-7.46 (-25.20, 10.6)	-0.51 (-0.85, -0.16)			-1.0% (-11.6%, 9.6%)	1.8% (-11.8%, 15.4%)	-0.4% (-4.6%, 3.8%)	-0.7% (-4.9%, 3.6%)		-0.95 (-7.37, 5.48)	

Classification of the intervention (color)			Certainty of the evidence (CoE) (Shading)
Among most beneficial	Among least beneficial / no clear effect compared to placebo	No data (blank)	High/Moderate CoE (Solid)
Among most harmful			Low/Very Low CoE (Shaded)

FIG 1. INCS summary of findings table.[1] *AE*, Adverse event; *CoE*, certainty of evidence; *EDS*, exhalation delivery system; *HRQoL*, health-related quality of life; *VAS*, visual analog score.

4. Investigator-led RCTs, independent of industry influence and analysis, addressing patient-important questions.
5. See the linked systematic review and NMA that outlines other research priorities.[9]
6. Cost-effectiveness of treatment options.

Question 3: Should ATAD, rather than no ATAD, be used in people with AERD?

Summary of the evidence, benefits, and harms. Summary of findings and the EtD table for this question, Table E5 (in this article's Online Repository at www.jacionline.org), are posted in the Online Repository (see also Fig 2). For this question we updated the systematic review that was identified from 2019[7] for information up to September 1, 2021.

ATAD improves disease-specific quality of life as measured on the SNOT-22 scale by a MD of −10.61 (95% CI: −14.51, −6.71) compared to placebo. This point estimate is higher than the prespecified minimally significant difference for the SNOT-22 scale of 8.9, which was the prespecified MID set by the work group when considering the available literature.[15,16] ATAD improves nasal symptoms score as measured on a 0- to 10-point scale by −2.74 (95% CI: −3.92, −1.57) compared to placebo.[7,9] This point estimate is higher than the MID for the symptom score scale of 1.0, suggesting that the average person taking this intervention is likely to have a patient-important improvement in nasal obstruction. Optimal timing of ATAD is not known; studies included in these analyses were performed closely following surgery (where ATAD would be used to prevent polyp regrowth) or when no recent surgery was performed (where ATAD would be used to reduce existing polyp burden). Adverse events were more common in people who took aspirin compared to placebo. The relative risk of having an adverse event was 3.84 (95% CI: 1.11, 13.22).[7] For every 10 people treated with aspirin, 1 will have an adverse event serious enough to stop treatment with aspirin.[7] For every 12 people treated with aspirin, 1 will have gastritis (irritation of stomach lining).[7] In the 75 people assessed in the trials of aspirin for AERD, 2 in the aspirin treatment group had major GI bleeding and none in the placebo group. The risk of long-term bleeding with aspirin is well-established by a large body of cardiovascular research. Even when lower dose aspirin (81 mg) was used in people for primary prevention, increased odds for harm were found: odds ratio (OR) of 1.44 (95% CI: 1.32, 1.57) for total major bleeding, OR of 1.53 (95% CI: 1.39, 1.70) for extracranial bleeding, OR of 1.58 (95% CI: 1.38, 1.80) for major GI bleeding, and OR of 1.31 (95% CI: 1.11, 1.54) for intracranial bleeding.[22] Consequently, primary prevention of cardiovascular diseases using aspirin is becoming more selective due to recognition of the harms of chronic aspirin use.[30] The guideline panel notes that doses of aspirin used for ATAD are higher than the 81 mg used for cardiovascular disease and could increase the risk of harm further.[31,32] The optimal dose of aspirin for ATAD is not clear and most clinical trials used 650 to 1300 mg per day.[9]

Assumed values and preferences. Panel members agreed that there is probably uncertainty in the value and importance patients put on the critical outcomes of disease-specific quality

	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40) †	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 13.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)				Certainty (shading)
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

HRQoL, health-related quality of life; SNOT-22, sino-nasal outcome test 22; VAS, visual analog score; UPSIT, University of Pennsylvania Smell Identification Test; OCS, oral corticosteroids; CT, computed tomography; LMK, Lund-Mackay
*The expected risk of each outcome with standard care is reported in the grey row
Numbers in the colored cells are the estimated mean differences (95%CI) for HRQoL, symptoms, smell, nasal polyp size and CT score and absolute risk differences (95%CI) per 100 patients (with accompanying relative risks [95% CI]) for rescue OCS, rescue nasal polyp surgery and adverse events versus standard care.

†The only scale presented where higher is better. Higher scores indicate worse outcome for all other scales shown.
GRADE certainty
High certainty – Further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty – Any estimate of effect is very uncertain

FIG 2. ATAD and biologics summary of findings table.[4] *ASA*, Acetylsalicylic acid; *CT*, computed tomography; *LMK*. Lund-Mackay; *OCS*, oral corticosteroids.

of life and nasal symptoms scores. For detailed consideration of values and preferences, acceptability of interventions, feasibility of implementation, and required resources, please see the EtD table (Table E5).

Balance between desirable and undesirable health effects. Panel members thought that the overall balance of effects favored ATAD. However, they acknowledged that using ATAD depends on values and preferences of people and/or their caregivers for individual outcomes. For those who value the improvement in disease-specific quality of life and nasal symptoms more than risks of the GI side effects and increased bleeding, the balance may favor ATAD use. For those who place more value on avoiding GI side effects and bleeding (including GI or intracranial), the balance may favor not using ATAD and instead weighing other AERD management options. Other management options for AERD include INCS, surgery, biologics, and/or anti-leukotrienes.

Recommendation. In people with AERD, the guideline panel suggests ATAD rather than no ATAD (conditional recommendation based on moderate certainty of evidence).

Remarks. The main factor driving recommendation type is the close balance of patient-important benefits and harms. Conditions that may be important during shared decision making are the risks that impact safety of desensitization such as poorly controlled asthma and the risks that impact safety of long-term aspirin use such as conditions or treatments that increase bleeding risk (age, male sex, smoking, diabetes, hypertension, systemic corticosteroid [eg. prednisone] use, and lower weight or body mass index).[32-34] Aspirin desensitization alone (without subsequent daily aspirin therapy) is thought to be ineffective for patients with AERD. This recommendation applies only to patients with CRSwNP who have AERD. It does not apply to patients with CRSwNP with aspirin-sensitivity that is not AERD.

Implementation considerations. In all cases, the diagnosis of CRSwNP must be confirmed by using appropriate diagnostic tools including direct visualization of nasal polyps with nasal endoscopy.[11,12] To consider ATAD, patients should have a diagnosis of AERD, which means a convincing history of a respiratory reaction to aspirin or nonsteroidal anti-inflammatory drugs (as judged by the clinician) or the development of respiratory symptoms during an aspirin challenge. Conducting an aspirin desensitization requires training of staff and a setting where reactions can be managed. Patients and their families require specific education, including advice about what to do if they need a procedure that requires temporary cessation of aspirin use. When choosing to prescribe ATAD, clinicians should discuss both the risks associated with the desensitization as well as long-term aspirin use. Also, when choosing to use ATAD, clinicians need to monitor clinical symptoms, medication adherence, and provide ongoing advice about aspirin dosing. Furthermore, clinicians should monitor for adverse effects of long-term aspirin use.

Implications for further research. When reviewing the evidence and considering all other factors influencing this recommendation, the guideline panel identified the following priorities for further research:

1. Large RCTs of ATAD to clarify the uncertainty of effects on sense of smell, systemic corticosteroid use, and rescue surgery outcome as well as frequency of adverse reactions.
2. Large, well-conducted and reported RCTs of active treatments (eg, ATAD vs various biologics) as well as RCTs of combined treatment with aspirin and biologics.
3. As described for INCS and biologics, robust studies addressing which outcomes are important to patients and the most credible MIDs for these outcomes.
4. See the linked systematic review and NMA for other research priorities.[7]

DISCUSSION

Strengths and limitations of these guidelines

These guidelines help support evidence-based decision making by clinicians, patients, and their family members. The strength of these guidelines is in the diverse guideline panel including clinicians treating people with CRSwNP, researchers, and patients; the process of using systematic reviews of available evidence to inform recommendations; and using the GRADE approach to develop recommendations. Additional efforts to minimize bias included a process for managing conflicts of interest, *a priori* outcome selection, *a priori* outcome threshold selection, and submission of the study protocols on publicly available web sites. These are standards of trustworthy guidelines and optimal translation of evidence to patient care.[35]

However, the evidence that informs these guidelines has important limitations. These are discussed in detail in the implications for research sections as well as the linked systematic reviews.[7-9] Recommendations about the use of ATAD and biologics are based on moderate certainty of evidence and for INCS, low certainty of evidence—the lowest certainty estimates were in quality of life and harms. Thus, future RCTs focusing on all patient-important outcomes, rather than primarily nasal obstruction or surrogate outcomes of nasal polyp size, are critical to address how to best use these interventions. Recommendations about the use of ATAD, INCS, and biologics must be individualized; the best choice for individual patients will depend on several conditions listed in the remarks section. While we generated recommendations at the individual level, robust research focused on cost-effective analyses, and implementation will help guide future decisions about these treatments at the population level. It is critical that such analyses are free from industry influence to generate unbiased estimates. Finally, these guidelines did not compare INCS and biologics as competing choices nor do they include all potential treatments for CRSwNP including surgery. Almost all the trials for biologics included INCS as standard of care in all study arms. While it may be possible to perform a NMA that includes INCS and biologics to compare these choices, the CRSwNP work group elected against pursuing this after discussion.

What others are saying and what is new in these JTF-PP guidelines

The most recent JTF-PP guideline for rhinosinusitis was published in 2014.[4] The 2014 guideline listed 47 summary statements encompassing multiple diagnostic and therapeutic questions. The 2014 guidelines used a now outdated rating of the medical evidence and wording of recommendations including strong recommendation, recommendation, option, and no recommendation. INCS for CRSwNP was listed as a strong recommendation in 2014 based on evidence from RCTs; there was no structured appraisal using GRADE. ATAD and biologics (listed separately as anti–IL-5 and anti-IgE) were listed as recommended based on evidence that was extrapolated from controlled studies. Several of the trials used to inform the current guideline were performed after 2014, particularly for ATAD and biologics. The differences between the 2014 and 2022 guideline statements reflect this updated information, the more limited scope of the 2022 guideline focused on 3 key questions, the focus on patient-important outcomes, and the decision to adhere to stringent standards for evidence-based medicine using systematic reviews of the evidence and interpretation and translation into recommendations using GRADE.[3] For example, the GRADE approach allows for considerations of multiple aspects of randomized trials, including risk of bias, imprecision, indirectness, inconsistency, publication bias, among others. The small effect size across patient-important outcomes among all INCS modalities, low certainty evidence, and consideration about patient values and preferences warranted the more appropriate conditional recommendation. We now provide explicit key conditions to consider that patients and clinicians should discuss in a shared

TABLE III. Conditions important for shared decision making

1. INCS[8]

Clinical outcomes (comparison of different modalities: stent, spray, rinse, EDS, drops, nebulizer, injection vs placebo)

- Rinses and EDS improve quality of life
- Sprays, EDS, and stent improve symptoms
- Stent, spray, EDS, and drops improve smell
- Spray, EDS, and stent may reduce need for rescue surgery

Adverse effects

- No different than placebo

Additional issues: spray is over the counter and cost is not prohibitive to most

2. Biologics[9]

Clinical outcomes (comparison of benralizumab, dupilumab, mepolizumab, omalizumab vs placebo)

- Quality of life: dupilumab > omalizumab > mepolizumab > benralizumab
- Symptoms: dupilumab > omalizumab > mepolizumab
- Smell: dupilumab > mepolizumab > omalizumab > benralizumab
- Decrease in need for OCS: dupilumab > mepolizumab > benralizumab
- Decrease in need for surgery: dupilumab > mepolizumab > omalizumab

Adverse effects

- No different than placebo

Additional issues: very costly, needs long-term treatment, no comparison with surgery and whether it should be used with, before, or after surgery. May be considered more favorably in those with other comorbidities that are treated with biologics.

3. ATAD in patients with AERD[9]

Clinical outcomes compared to placebo

- Improves symptoms and quality of life
- No different than placebo for smell
- May not decrease need for OCS or rescue surgery

Adverse effects

- Bleeding risk and GI side effects more common than placebo (for every 10 people treated with ATAD, 1 will have an adverse sufficiently event enough to stop treatment)

Additional issues: affordable, long-term treatment

decision-making model to identify the optimal, individualized treatments.

Two other recent clinical guidelines comment on use of ATAD, INCS, and biologics for CRSwNP.[11,12] The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 advises use of INCS for CRSwNP but does not advise a specific delivery method because they did not have any comparative analyses available to them.[12] Furthermore, EPOS 2020 considers INCS stents as a separate category and suggests they be used as an option. The JTF-PP guideline instead uses NMA to inform the comparative efficacy and safety of the various INCS delivery methods using a rigorous and transparent method.[8] Per EPOS 2020, ATAD can be a treatment for AERD for people who are likely to be compliant to therapy and biologics can be used according to criteria used in the clinical trials (for dupilumab and anti–IL-5 biologics) with insufficient data at that time to advise on omalizumab. Additional data since 2020 on biologics are now available and incorporated into the NMA that informed JTF-PP 2022 recommendations addressing all biologics available in routine practice and ATAD.

The second recent clinical guideline is the International Consensus on Rhinology and Allergy: Rhinosinusitis (ICAR-RS) 2021, which gives a strong recommendation for use of INCS spray and rinse for CRSwNP based on as assessment of multiple RCTs and an option to use INCS exhaled delivery system.[11] In addition, ICAR-RS 2021 recommends dupilumab for severe CRSwNP and an option to use other biologics. ATAD is recommended by ICAR-RS. Taken together, the conditional recommendations and linked considerations made in JTF-PP 2022 have some important differences from prior guidelines, primarily based on new available information and differences in methodology to assess the evidence.

Finally, to make the recommendations from this guideline more useful, a table including a summary of key factors for shared decision making is included (Table III).

Revision or adaptation of these guidelines

After publication of these guidelines, the JTF-PP will maintain them through surveillance for new evidence, ongoing review by experts, and updates as needed.

Adaptation of these guidelines may be necessary in many circumstances. We encourage all stakeholders who would like to adapt the recommendations to their local circumstances to use the EtD tables in the Online Repository and to follow the systematic and transparent GRADE–Adaptation, Adoption, *De Novo* Development (GRADE-ADOLOPMENT) process, which encourages adoption, adaptation, and when needed, the development of new guidelines.[36]

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