SINUSITIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- December 2023

To the CHI Original Sinusitis Clinical Guidance- Issued November 2019

Contents

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Abbreviations

AECRS	Acute Exacerbation of CRS
AERD	Aspirin-Exacerbated Respiratory Disease
AFRS	Allergic Fungal Rhinosinusitis
AMT	Appropriate Medical Therapy
ARS	Acute Rhinosinusitis
ATAD	Aspirin Therapy After Desensitization
BSD	Balloon Sinus Dilation
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CI	Confidence interval
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without Nasal Polyps
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CT	Computed Tomography
DBPCT	Double Blind Placebo-Controlled Trial
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ESS	Endoscopic Sinus Surgery
HAS	Haute Autorite de Sante
HTA	Health Technology Assessment
INCS	Intranasal Corticosteroid
LK	Lund-Kennedy
MAST	Maxillary Antrostomy Sinus Tubes
MFNS	Mometasone Furoate Nasal Spray
MSS	Major Symptom Score

NMA	Network Meta-Analysis
NPS	Nasal Polyp Score
OCS	Oral Corticosteroids
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality of Life
RCT	Randomized Controlled Trial
RS	Rhinosinusitis
SFDA	Saudi Food and Drug Authority
SMD	Standard Mean Difference
SNOT-22	Sino-Nasal Outcome Test-22

Executive Summary

Sinusitis is characterized by inflammation of the lining of the paranasal sinuses. Because the nasal mucosa is simultaneously involved, and because sinusitis rarely occurs without concurrent rhinitis, rhinosinusitis is the preferred term for this condition. It is more common in females, and the highest incidence is between the ages 45 to 64 years[1].

Clinical findings in acute sinusitis may include the following: pain over cheek and radiating to frontal region or teeth, increasing with straining or bending down, Redness of nose, cheeks, or eyelids, tenderness to pressure over the floor of the frontal sinus immediately above the inner canthus, referred pain to the vertex, temple, or occiput, postnasal discharge, a blocked nose, persistent coughing or pharyngeal irritation, facial pain, hyposmia[1].

Symptoms of acute bacterial rhinosinusitis include facial pain or pressure (especially unilateral), hyposmia/anosmia, nasal congestion, nasal drainage, postnasal drip, fever, cough, fatigue, maxillary dental pain, ear fullness/pressure[1].

The etiology and types of sinusitis are described below:

- **Acute viral rhinosinusitis**: Most rhinosinusitis episodes are caused by viral infection. Most viral upper respiratory tract infections are caused by rhinovirus, but coronavirus, influenza A and B, parainfluenza, respiratory syncytial virus, adenovirus, and enterovirus are also causative agents[1].
- **Acute bacterial rhinosinusitis** is very frequently associated with viral upper respiratory tract infection, although allergy, trauma, neoplasms, granulomatous and inflammatory diseases, midline destructive disease, environmental factors, dental infection, and anatomic variation, which may impair normal mucociliary clearance, may also predispose to bacterial infection. The most common pathogens isolated from maxillary sinus cultures in patients with acute bacterial rhinosinusitis include *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. *Streptococcus pyogenes, Staphylococcus aureus, and* anaerobes are less commonly associated with acute bacterial rhinosinusitis[1].
- **Purulent sinusitis** can occur when ciliary clearance of sinus secretions decreases or when the sinus ostium becomes obstructed, which leads to retention of secretions, negative sinus pressure, and reduction of oxygen partial pressure. This environment is then suitable for growth of pathogenic organisms. Factors that predispose the sinuses to obstruction and decreased ciliary function are allergic, nonallergic, or viral insults, which produce inflammation of the nasal and sinus mucosa and result in ciliary dysmotility and sinus obstruction[1].

- **Acute invasive fungal rhinosinusitis***:* Rarely, sinusitis is caused by fungi. Fungal sinusitis (e.g., allergic fungal sinusitis) may appear similar to lower airway disorder and allergic bronchopulmonary aspergillosis. Fungal agents associated with this condition
  include Aspergillus and Alternaria species. Bipolaris and Curvularia species are the most common fungi recovered in allergic fungal sinusitis[1].

Acute sinusitis doesn't often cause complications. Complications that might happen include[2]:

- **Chronic sinusitis**: acute sinusitis can be a flare-up of a long-term problem known as chronic sinusitis. Chronic sinusitis lasts longer than 12 weeks.
- **Meningitis**: this infection affects the membranes and fluid around the brain and spinal cord.
- **Other infections**: although uncommon, an infection can spread to the bones, known as osteomyelitis, or to skin, known as cellulitis.
- **Vision problems**: if the infection spreads to the eye socket, it can reduce vision or cause blindness.

Acute sinusitis is a clinical diagnosis. However, the evaluation might include the following laboratory tests: nasal cytology, nasal-sinus biopsy, tests for immunodeficiency, cystic fibrosis, or ciliary dysfunction. Nasal cytology examinations may be useful to elucidate the following entities: allergic rhinitis, eosinophilia, nasal polyposis, aspirin sensitivity. Tests for immunodeficiency are indicated if history findings indicate recurrent infection; they include the following: immunoglobulin studies, HIV serology. Cultures are not routinely obtained in the evaluation of acute sinusitis but should be obtained in the following cases: patients in intensive care or with immunocompromise, children not responding to appropriate medical management, patients with complications of sinusitis. In adults, cultures are directed at the middle meatus. Aspiration of the sinus by direct antral puncture is the only accurate way to obtain a culture but is reserved for patients with any of the following: Life-threatening illness, Immunocompromise. Disease unresponsive to therapy. Computed tomography (CT) scanning is the preferred imaging method for rhinosinusitis. A complete sinus CT scan with frontal and coronal planes is used if an alternative diagnosis (e.g., tumors) must be excluded. CT scanning is characteristic in allergic fungal sinusitis and is one of the major criteria for diagnosis[1].

Most cases of acute sinusitis get better on their own. Self-care is usually all that's needed to ease symptoms. The following might help ease sinusitis symptoms: Saline nasal spray, nasal corticosteroids, decongestants, allergy medicines, pain relievers. Antibiotics don't treat viruses, which are the usual cause of acute sinusitis. Even if bacteria caused the acute sinusitis, called a bacterial infection, it might clear up on its own. So, a health care provider might wait and see if the acute sinusitis gets worse

before prescribing antibiotics. For sinusitis caused or made worse by allergies, allergy shots might help. This is known as immunotherapy[2].

Acute rhinosinusitis accounts for 1 in 5 antibiotic prescriptions for adults, making it the fifth most common reason for an antibiotic prescription. Approximately 6% to 7% of children with respiratory symptoms have acute rhinosinusitis. An estimated 16% of adults are diagnosed with ABRS annually. Given the clinical nature of this diagnosis, there is a possibility of overestimation.

An estimated 0.5 to 2.0% of viral rhinosinusitis (VRS) will develop into bacterial infections in adults and 5 to 10% in children[3].

The prevalence of CRS ranges between 6% and 27.1%; the prevalence of CRS in the United States is 12% and in Europe is 10.9%. However, the prevalence of CRS in Saudi Arabia is 25.3%[4].

CHI issued Sinusitis guidelines in November 2019. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. below is a description of sections that need updates.

This report functions as an addendum to the prior CHI Sinusitis clinical guidance and seeks to offer guidance for the effective management of Sinusitis. It provides an **update on the Sinusitis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the updated guidelines added to the report such as** international consensus statement on allergy and rhinology: rhinosinusitis 2021, The guideline; Adult Sinusitis, was developed by the American Academy of Otolaryngology-Head and Neck Surgery and was reviewed and categorized as Affirmation of Value by the American Academy of Family Physicians. (*Affirmation of Value*, April 2020) and **the new guidelines added to the report** such as European Position Paper on Rhinosinusitis and Nasal Polyps [2020], The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis [2023], The chronic rhinosinusitis practice parameter. *Ann Allergy Asthma Immunol* [2023], Nasal Irrigation for Chronic Rhinosinusitis in Adults. *Clin Exp Otorhinolaryngol* [2022]**,** British Rhinological Society Consensus Guidance on the use of biological therapies for chronic rhinosinusitis with nasal polyps [2021], the Canadian consensus on the use of biologics in upper airway [2023].

After carefully examining clinical guidelines and reviewing the SFDA drug list, there are new SFDA registered drugs to include in the CHI formulary dupilumab and omalizumab, while removing: AMOXICILLIN, CLAVULANIC ACID 125,31.25 mg, mg ORAL SUSPENSION - AMOXICILLIN, CLAVULANIC ACID 250,62.5 mg ORAL SUSPENSION - CLAVULANIC ACID 62.5 mg, Powder for oral suspension -

PARACETAMOL 500 mg, Capsule as they are no longer registered on the SFDA Drug List of September 2023. There have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits since November 2019.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Sinusitis therapeutic management.

Below is a table summarizing the major changes based on the different Sinusitis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Sinusitis

Management of Sinusitis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Intranasal Corticosteroids (INCS): INCS should be used as monotherapy in mild to moderate ARS or as adjuvant to antibiotic therapy in severe cases of ARS.	Policy Level: Use of INCS: Strong recommendation	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021
Chronic Rhinosinusitis without Nasal Polyps (CRSsNP): Saline nasal irrigation improves symptoms, QoL and nasal endoscopy for patients with CRSsNP. Duration of treatment should be greater than 8 weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated saline (40◦c) over room temperature saline. Devices with volume greater than 60 mL bring greater benefits.	Policy Level: Recommendation	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021
Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) Oral Corticosteroids: Strong recommendation for the use of oral	Policy Level: Strong recommendation for short-term use	International Consensus Statement on Rhinology and

corticosteroids in the short-term management of CRSwNP. Longer term use of steroids for CRSwNP is not supported by the literature and carries an increased risk of harm to the patient.		Allergy: Rhinosinusitis, 2021
<u>Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)</u> • Dupilumab: Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options.	Policy Level: Recommendation for dupilumab in patients with severe CRSwNP.	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021
• Omalizumab: Consider for severe CRSwNP with concomitant poorly controlled allergic asthma	Policy Level: Option to weak recommendation for patients with severe CRSwNP who have not improved despite other medical and surgical treatments. Weaker recommendation is based on limited body of evidence and high cost.	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021
<u>Aspirin Desensitization for AERD</u> • Aspirin desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence.	Policy Level: Recommendation	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021
<u>AFRS (Allergic Fungal Rhinosinusitis) Management</u> • Antifungal Therapy: Can consider topical or oral antifungals in AFRS patients recalcitrant to maximal topical steroid therapy and	Policy Level: Option	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021

immunotherapy. Policy Level: Option • Immunotherapy: Immunotherapy remains a reasonable treatment option. Policy Level: Option. • Anti-IgE: Consider use in difficult to treat AFRS patients with persistent thick mucoid and inflammatory discharge despite topical steroid therapy. Policy Level: Option		
Pediatric Rhinosinusitis (PCRS) • Given the likely viral etiology, antibiotics should not be given for the first 10 days of uncomplicated acute rhinosinusitis: Antibiotics should not be given for the first 10 days of uncomplicated ARS: Policy Level: Recommendation. • For patients without penicillin allergy, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as 2 nasal symptoms lasting greater than 10 days, or acute onset of severe symptoms): For patients without penicillin allergies, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as 2 nasal symptoms lasting greater than 10 days). Policy Level: Recommendation.	Policy Level: Recommendation	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis, 2021
Nasal saline irrigation: Clinicians should recommend nasal saline irrigation to patients with chronic sinusitis or those who have undergone endoscopic sinus surgery	Strong recommendation	Nasal Irrigation for Chronic Rhinosinusitis in Adults. Clin Exp Otorhinolaryngol, 2022
Irrigation solution preparation: Clinicians should recommend an	Recommendation	Nasal Irrigation for Chronic

appropriate irrigation fluid preparation method for patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. For irrigation fluid, bottled or distilled water should preferably be used. If tap water is used, boil it for at least 5 minutes and cool before use or expose it to ultraviolet light for at least 45 seconds.		Rhinosinusitis in Adults. Clin Exp Otorhinolaryngol, 2022

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in the **clinical and therapeutic management of sinusitis.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Sinusitis report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the November 2019 CHI Sinusitis Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 **NICE** Guidelines for Acute Sinusitis (Antimicrobial Prescribing) [**2017**]	N/A*
1.2 **American Academy of Otolaryngology– Head and Neck Surgery** Clinical Practice Guideline: Adult Sinusitis [**2015**]	Section 1.1.1 The guideline, Adult Sinusitis, was developed by the American Academy of Otolaryngology-Head and Neck Surgery and was reviewed and categorized as Affirmation of Value by the **American Academy of Family Physicians** (**Affirmation of Value**, April **2020**)[5]
1.3 **American College of Physicians** and the **Centers for Disease Control and Prevention** Practice Guideline for Appropriate Antibiotic Use for acute Respiratory Tract Infection in Adults [**2016**]	N/A*
1.4 **Saudi National Antimicrobial Therapy** Guidelines for Community and Hospital Acquired Infections in Adults [**2018**]	N/A*

1.5 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (**ICAR-RS**) [**2016**]	Section 1.1.2 International Consensus Statement on Rhinology and Allergy: Rhinosinusitis (**ICAR-RS**) [**2021**]
1.6 **American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology** Practice Parameter Update on the Diagnosis and Management of Rhinosinusitis [**2016**]	N/A*

*: *No updated versions available*

1.1.1 American Academy of Otolaryngology– Head and Neck Surgery Sinusitis Guidelines (American Academy of Family Physicians Affirmation of Value, 2020)

*Please refer to **Section 1.2** of CHI Sinusitis original clinical guidance.*

This clinical guideline on the management of adult sinusitis was developed in 2015 by the American Academy of Otolaryngology-Head and Neck Surgery and was reviewed and categorized as "affirmation of value" by the American Academy of Family Physicians (AAFP) in April 2020[5]. The main recommendations are summarized below:

- Acute bacterial rhinosinusitis (ABRS) should be distinguished from acute rhinosinusitis due to viral respiratory infections and noninfectious conditions. ABRS should be diagnosed when signs and symptoms of acute rhinosinusitis (ARS) (purulent nasal drainage plus nasal obstruction, facial pain-pressure, or both) persist without improvement for at least 10 days or if signs and symptoms worsen within 10 days after initial improvement.
- Radiographic imaging should *not* be performed in patients with ARS unless a complication or alternative diagnosis is suspected.
- Analgesics, intranasal steroids and/or nasal saline irrigation may be recommended for symptomatic relief of viral or bacterial rhinosinusitis.
- Adults with uncomplicated ABRS should be either offered watchful waiting or prescribed antibiotic therapy. Patients undergoing watchful waiting should be prescribed antibiotics if their symptoms fail to improve after 7 days or worsen at any time.

- If a decision is made to treat ABRS with antibiotics, amoxicillin with or without clavulanate should be prescribed as first-line therapy for 5-10 days. Amoxicillin with clavulanate should be prescribed for patients at high risk of being infected by an organism resistant to amoxicillin.
- Patients with an allergy to penicillin should be prescribed doxycycline or a respiratory quinolone as first-line therapy.
- For patients who fail to improve or worsen by 7 days following initial treatment, they should be reassessed to confirm the diagnosis and to detect complications. If initial treatment involved watchful waiting, antibiotics should be prescribed. If initial treatment included an antibiotic, a different antibiotic should be prescribed.
- Chronic rhinosinusitis (CRS) and recurrent acute rhinosinusitis should be distinguished from isolated episodes of ABRS.
- The diagnosis of CRS should be confirmed with documentation of sinonasal inflammation using anterior rhinoscopy, nasal endoscopy, or computed tomography.
- Saline nasal irrigation, intranasal corticosteroids, or both should be prescribed for symptom relief in patients with CRS.
- Testing for allergy and immune function may be obtained when evaluating a patient for CRS or recurrent ARS.
- Antifungal therapy for CRS. Clinicians should not prescribe topical or systemic antifungal therapy for patients with CRS.

1.1.2 International Consensus Statement on Rhinology and Allergy: Rhinosinusitis [2021]

*Please refer to **Section 1.5** of CHI Sinusitis original clinical guidance.*

The 5 years since the publication of the first International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS) has witnessed foundational progress in the understanding and treatment of rhinologic disease. The 2021 revised edition introduced a set of recommendations accompanied by a grading scheme, outlined as follows[6]:

Table 3. American Academy of Pediatrics (AAP) Defined Strategy for Recommendation Development

Level of Evidence	Diagnosis	Therapy/Prevention/Etiology
1	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Systematic review of randomized trials or n-of-1 trials
2	Individual cross-sectional studies with consistently applied reference standard and blinding	Randomized trial or observational study with dramatic effect
3	Cohort study or control arm of randomized trial	Non-randomized controlled cohort/follow-up study
4	Case-series or case control studies, or poor quality prognostic cohort study	Case-series, case-control studies, or historically controlled studies*
5	Not applicable	Mechanism-based reasoning

*Level may be graded down on the basis of study design, inconsistency between studies, indirectness of evidence, imprecision, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size or if a significant dose-response relationship is demonstrated. **As always, a systematic review is generally better than an individual study

Aggregate grade of evidence	
Grade	**Research Quality**
A	Well-designed RCTs
B	RCTs with minor limitations Overwhelming consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Expert opinion Case reports Reasoning from first principle

AAP (American Academy of Pediatrics) defined strategy for recommendation development			
Evidence Quality	**Preponderance of Benefit over Harm**	**Balance of Benefit and Harm**	**Preponderance of Harm over Benefit**

A. Well-designed RCT's	Strong recommendation	Option	Strong Recommendation Against
B. RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies	Recommendation		Recommendation Against
C. Observational studies (case control and cohort design)			
D. Expert opinion, Case reports, Reasoning from first principles	Option	No Recommendation	Recommendation Against

- ➔ ICAR-RS-2021 provides a critical review of the diagnosis, pathophysiology, management, and complications of Acute RS (ARS), Recurrent ARS, Chronic RS (CRS) with and without nasal polyps (CRSwNP and CRSsNP), Acute Exacerbation of CRS (AECRS), and Pediatric RS. While the most up-to-date evidence has been incorporated into each of these areas, the novel application of biologic therapies for CRSwNP has emerged as perhaps the most informative.
- ➔ RS is divided and defined based on the temporal course of its manifestation. Diagnosis of CRS requires confirmation of both subjective and objective criteria.

The following algorithm shows the diagnostic algorithm for rhinosinusitis:

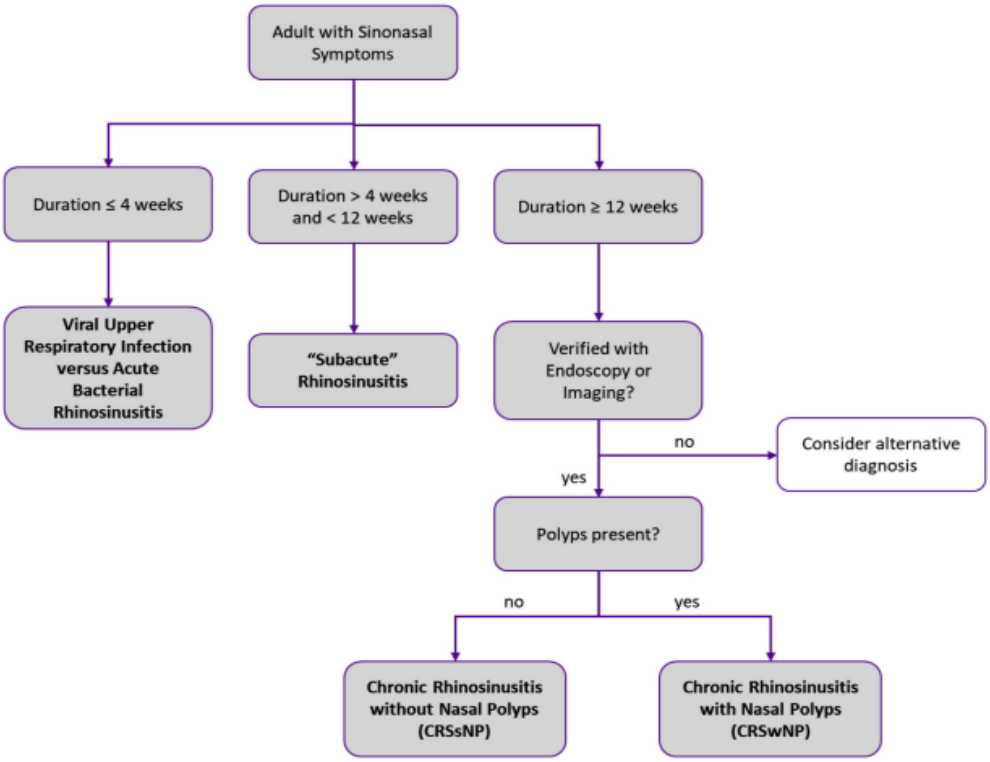

Figure 1. *Diagnostic Algorithm for Rhinosinusitis. Retrieved from ICAR-RS 2021.*

Management of Acute Rhinosinusitis (ARS)

- Antibiotic therapy for ARS: consider initial watchful waiting in uncomplicated cases, with institution of antibiotic therapy if no improvement after 7 days or worsening at any time, or for mitigating circumstances as noted above. Policy Level: Option.
- Corticosteroids:
    - ➔ Intranasal corticosteroids (INCS): INCS should be used as monotherapy in mild to moderate ARS or as adjuvant to antibiotic therapy in severe cases of ARS. Policy Level: Use of INCS: Strong recommendation.
    - ➔ Oral corticosteroids: systemic corticosteroids may be useful with severe facial pain or headaches secondary to ARS, otherwise no tangible benefit. No role as monotherapy for ARS. Policy Level: No recommendation
- Topical Saline Spray and Irrigation: Saline irrigation may be used in adjunct with antibiotics for ABRS. Policy Level: Option
- Decongestants and Other Adjunctive Treatments:

➔ Decongestants are an option in ABRS, as they can reduce congestion in patients with ABRS; however, side effects should be considered. Policy Level: Option.

- Antihistamines are an option in ABRS with comorbid AR and can be used to decrease symptoms of AR. Policy Level: Option
- Mucolytics: Based on the current evidence, no recommendation can be given for mucolytics in ABRS. Policy Level: No recommendation
- Herbal Remedies: None. Side effects should be considered if used. Policy Level: No recommendation

Management of RARS (Recurrent Acute Rhinosinusitis)

- Option for use of INCS spray for sinonasal symptoms during acute exacerbations of RARS. Policy Level: Option
- Endoscopic Sinus Surgery: ESS (Endoscopic Sinus Surgery) or BSD (Balloon Sinus Dilation) is recommended for patients with RARS. Policy Level: Recommendation

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)

<u>Diagnosis</u>

- *Establishing the Diagnosis of CRS*

  An algorithm can be used to diagnose CRS. Aside from the presence of 2 cardinal symptoms for ≥12 weeks, the addition of 1 objective finding on CT or nasal endoscopy greatly increases diagnostic accuracy. Policy Level: Recommendation.

- *Using Symptoms Alone to Diagnose CRS*

  Recommendation against using a “symptoms-alone” strategy to make the diagnosis of CRS. Policy Level: Recommend against.

- *Using Endoscopy to Diagnose CRS*

  Nasal endoscopy is recommended in conjunction with a history and physical examination for a patient being evaluated for CRS. CT is an option for confirming CRS along with or instead of nasal endoscopy. Policy Level: Recommendation

- *Using Imaging to Diagnose CRS*

  CT scanning is recommended for all patients meeting symptom-based criteria for CRS with a lack of objective clinical findings on anterior rhinoscopy

or nasal endoscopy, or for preoperative planning. It is an option for confirming CRS instead of nasal endoscopy. Policy Level: Recommendation

Management

- Saline nasal irrigation improves symptoms, QoL and nasal endoscopy for patients with CRSsNP. Duration of treatment should be greater than 8 weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated saline (40◦c) over room temperature saline. Devices with volume greater than 60 mL bring greater benefits. Policy Level: Recommendation
- Topical Corticosteroids: Standard Delivery (Sprays): Standard metered dose INCS could be used in treatment of CRSsNP, particularly if primary symptoms are that of rhinitis. Policy Level: Option
- Intranasal Corticosteroids (Nonstandard Delivery) for CRSsNP: Corticosteroid nasal irrigations are recommended in CRSsNP in postoperative patients and an option in nonsurgical/medical therapy patients. The use of atomizers/exhalational devices is an option. No recommendation for MAST. Policy Level: Irrigations – Recommended in postoperative patients, option for use in non-surgical/medical therapy patients. Atomizers/exhalational devices - Option. MAST – No recommendation
- Oral Corticosteroids: The use of oral corticosteroid in CRSsNP is an option and should be individualized based on patient preference and co-morbidities. Recommendation Level: Option
- Macrolide Antibiotics: Macrolides are an option for patients with CRSsNP, especially for patients at low risk of harm. Policy Level: Option
- Intravenous Antibiotics: Intravenous antibiotics should not be used for routine cases of CRS. For extenuating circumstances such as nonoperative patients, those who have failed oral/topical therapy, or those with extranasal manifestations of CRS the benefits of treatment may outweigh the risks. Policy Level: Recommendation against.
- Topical Antibiotics: Topical antibiotics are not recommended for routine CRS. They may be beneficial in unusual circumstances. Policy Level: Recommendation against.
- Topical Antifungals: Topical antifungal agents are not recommended for CRSsNP or CRSwNP. Policy Level: Strong Recommendation Against
- Anti-Leukotriene Therapy: Montelukast is an option for CRSsNP patients with an allergic component to their disease, as an adjunct to INCS. Policy Level: No recommendation for non-allergic CRSsNP; Option for CRSsNP with comorbid allergy.

- Herbal Medications: Bias in data limits value judgments. Policy Level: No recommendation.
- Xylitol: Xylitol is an option for treating CRS. Policy Level: Option
- Colloidal Silver: Recommendation against use in CRS
- Capsaicin: Use of topical capsaicin as an adjunct treatment for CRS. Policy Level: Option

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Management

- Nebulized saline (5 mL) treatment is an option for treating CRSwNP, particularly patients with thick mucus. Policy Level: Option
- Intranasal Corticosteroids (Standard Delivery) for CRSwNP: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing or additional short-term corticosteroid drop if initial treatment effect is small. Policy Level: INCS: Strong Recommendation. Twice Daily Dosing: Option. High concentration/dose: No recommendation due to mixed and insufficient evidence.
- Intranasal Corticosteroids (Nonstandard Delivery) for CRSwNP: Following sinus surgery, those patients with CRSwNP that have moderate-severe disease or are not controlled with simple INCS should be offered corticosteroid irrigation and/or atomized delivery. Policy Level: Corticosteroid Irrigation: Strong Recommendation. Exhalation delivery: Option. Atomization/nebulization: Recommendation. Direct injection: No recommendation due to insufficient evidence.

Steroid Eluting Implants

- Corticosteroid-eluting implants can be considered as an option in a previously operated ethmoid cavity with recurrent nasal polyposis. Policy Level: Option
- Oral Corticosteroids: Strong recommendation for the use of oral corticosteroids in the short-term management of CRSwNP. Longer term use of steroids for CRSwNP is not supported by the literature and carries an increased risk of harm to the patient. Policy Level: Strong recommendation for short-term use

Oral Non-Macrolide Antibiotics for < 3 weeks

- Short courses (< 3 weeks) of non-macrolide antibiotics should generally not be prescribed for CRSwNP except in acute exacerbation. Policy Level: Recommendation against.

Oral Non-Macrolide Antibiotics for >3 Weeks

- Practitioners should weight the risks and benefits of extended courses (>3 weeks) of non-macrolide antibiotics for CRSwNP and know that the literature is sparse. Policy Level: No recommendation.

Macrolide Antibiotics

- In CRSwNP, macrolides may be beneficial, especially in neutrophil-dominant polyps or in those who are unresponsive to corticosteroids. Policy Level: Option.

Biologic Therapy

- **Dupilumab**: Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options. Policy Level: Recommendation for dupilumab in patients with severe CRSwNP.
- **Mepolizumab:** Consider as an option for severe CRSwNP with concomitant poorly controlled eosinophilic asthma. Policy Level: Option for patients CRSwNP and asthma
- **Reslizumab:** Can be considered as an option for severe CRSwNP with concomitant poorly controlled eosinophilic asthma. Policy Level: Option for patients with CRSwNP and asthma
- **Omalizumab:** Consider for severe CRSwNP with concomitant poorly controlled allergic asthma. Policy Level: Option to weak recommendation for patients with severe CRSwNP who have not improved despite other medical and surgical treatments. Weaker recommendation is based on limited body of evidence and high cost.

Anti-Leukotriene Therapy

- Montelukast is an option for CRSwNP patients either instead of or in addition to INCS. Policy Level: Option

Furosemide

- Topical furosemide started after ESS and in combination with an INCS may reduce the recurrence of nasal polyps in patients with CRSwNP. Policy Level: Option.

Aspirin Desensitization for AERD

- Aspirin desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence. Policy Level: Recommendation

Management of Allergic Fungal Rhinosinusitis (AFRS)

- Antifungal Therapy: Can consider topical or oral antifungals in AFRS patients recalcitrant to maximal topical steroid therapy and immunotherapy. Policy Level: Option
- Immunotherapy: Immunotherapy remains a reasonable treatment option. Policy Level: Option.
- Anti-IgE: Consider use in difficult to treat AFRS patients with persistent thick mucoid and inflammatory discharge despite topical steroid therapy. Policy Level: Option

Acute Exacerbation of Chronic Rhinosinusitis (AECRS)

In summary, clinical studies for the management of AECRS are still lacking and further high-quality studies are needed in this area. Because of the paucity of evidence, no recommendation is currently possible.

Indications for Sinus Surgery

Appropriate Medical Management: For CRSsNP: Appropriate medical therapy prior to surgical intervention should include INCS, saline irrigations, and antibiotics. Oral corticosteroids are an option. For CRSwNP: Appropriate medical therapy prior to surgical intervention should include a trial of INCS, saline irrigations, and a single short course of oral corticosteroids. Oral antibiotics are an option. Policy level: Recommendation, though weak based on strength of evidence.

Duration of Medical Therapy Prior to Surgery: A trial of 3-4 weeks of AMT should be considered as the minimum. Policy Level: Recommendation, though weak based on strength of evidence

Timing of Sinus Surgery: As part of a shared decision-making process with a patient, it is reasonable to avoid prolonged delays in offering surgery if appropriate medical therapy has failed to achieve adequate symptom control. At a health system level, patient pathways should be optimized to avoid unnecessary delays in surgery. Policy Level: Recommendation, though weak based on strength of evidence.

Preoperative Corticosteroids: INCS are recommended prior to ESS in CRSsNP. Policy level: Recommendation for INCS. No recommendation for oral corticosteroids.

Drug Eluting Stents in Sinus Surgery: Corticosteroid-eluting stents can be considered in the postoperative ethmoidectomy cavity. While the authors recognize the high cost of these implants, given the level of evidence, absorbable steroid-eluting implants are recommended in carefully selected patients that are like those included in the underlying clinical trials.

Postoperative Management following Sinus Surgery:

- The overall evidence supporting the use of saline irrigations remains grade B, and we make a recommendation for normal saline irrigations.
- The evidence for this treatment remains grade B, and we make a recommendation for postoperative outpatient debridement.
- The evidence remains grade A and supports a strong recommendation for the use of topical nasal steroids.
- The evidence remains level B, and we make a recommendation of option for use of antibiotics, citing both benefits and potential side effects.
- Topical decongestants. No new studies were identified in the review period which addressed topical decongestants. ICAR-RS-2016 review found insufficient evidence to support their use, and made a recommendation against topical decongestants, because of potential side effects and no clear benefit.1.2 Additional Guidelines
- There is Grade A evidence supporting the benefit in endoscopic appearance, and we make a recommendation for the use of steroid-eluting implants or spacers in select patients with CRS and / or nasal polyposis.

Pediatric Rhinosinusitis (PCRS)

<u>Management</u>

- Given the likely viral etiology, antibiotics should not be given for the first 10 days of uncomplicated acute rhinosinusitis: Antibiotics should not be given for the first 10 days of uncomplicated ARS: Policy Level: Recommendation.
- For patients without penicillin allergy, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as 2 nasal symptoms lasting greater than 10 days, or acute onset of severe symptoms): For patients without penicillin allergies, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as 2 nasal symptoms lasting greater than 10 days). Policy Level: Recommendation.
- PCRS management begins with medical therapy. Consensus exists that nasal saline irrigations (NSI) are beneficial in the pediatric population as a sole treatment modality or as a treatment adjunct.
- There is limited data regarding topical antibiotic irrigations for PCRS.
- Reports on the efficacy of INCS such as fluticasone or mometasone are conflicting due to a lack of proper clinical trials.

- Scientific evidence supporting the use of systemic antibiotics in PCRS is limited.
- Systemic corticosteroids have demonstrated clinical efficacy in the management of PCRS as an adjunct to systemic antibiotics.
- Contributing comorbid conditions, such as GERD, immunodeficiencies, PCD, and CF, may increase the complexity of PCRS management.
- Surgical intervention should be considered after appropriate medical therapy has failed.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Sinusitis report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
1.2.1 **European Position Paper** on Rhinosinusitis and Nasal Polyps [**2020**]
1.2.2 **American Academy of Allergy, Asthma & Immunology** (AAAAI) Joint Task Force on Practice Parameters GRADE Guidelines for the Medical Management of Chronic Rhinosinusitis with Nasal Polyposis [**2023**]
1.2.3 **American College of Allergy, Asthma & Immunology** Chronic Rhinosinusitis Practice Parameter [**2022**]
1.2.4 **Korean Society of Otorhinolaryngology-Head and Neck Surgery and Korean Rhinologic Society** Clinical Practice Guideline: Nasal Irrigation for Chronic Rhinosinusitis in Adults [**2022**]
1.2.5 **British Rhinological Society** (BRS) Consensus Guidance on the Use of Biological Therapies for Chronic Rhinosinusitis with Nasal Polyps [**2021**]
1.2.6 **Canadian Multidisciplinary Expert Consensus** on the Use of Biologics in Upper Airways: A Delphi Study [**2023**]

1.2.1 European Position Paper on Rhinosinusitis and Nasal Polyps [2020]

The European Position Paper on Rhinosinusitis and Nasal Polyps published in 2020 is the update of similar evidence-based position papers published in 2005 and 2007 and 2012. The core objective of the EPOS2020 guideline is to provide revised, up-to-date, and clear evidence-based recommendations and integrated care pathways in ARS and CRS[7].

Acute rhinosinusitis includes common cold and recurrent ARS in adults and children.

Treatment evidence and recommendations for adults and children with acute viral rhinosinusitis (common cold)

Antibiotics

- The EPOS2020 steering group, due to the low quality of the evidence, is uncertain whether or not the use of long-term antibiotics has an impact on patient outcomes in adults with CRS, particularly in the light of potentially increased risks of cardiovascular events. There is a need for the larger high-quality trials that are presently being undertaken in Europe.
- Topical antibacterial therapy does not seem to be more effective than placebo in improving symptoms in patients with CRS. However, it may give a clinically non-relevant improvement in symptoms, SNOT-22 and LK endoscopic score compared to oral antibiotics.
- Due to the very low quality of the evidence, it is uncertain whether or not the use of intravenous antibiotics therapy has an impact on patient outcomes in adults with chronic rhinosinusitis compared with placebo.
- Antibiotics [1a (-)]: There is no evidence of benefit from antibiotics for the common cold or for persisting acute purulent rhinitis in children or adults. There is evidence that antibiotics cause significant adverse effects in adults when given for the common cold and in all ages when given for acute purulent rhinitis. Routine use of antibiotics for these conditions is not recommended.

Corticosteroids

- Nasal corticostereoids have a positive impact on disease specific and general QOL in patients with CRS.
- Long term treatment with nasal corticosteroids is effective and safe in patients with CRS.
- The EPOS2020 steering committee advises to use nasal corticosteroids in patients with CRS. Based on the low to very low quality of the evidence for higher dosages or different delivery methods and the paucity of direct comparisons the steering committee cannot advise in favor of higher dosages or certain delivery methods.
- A short course of systemic corticosteroid, with or without local corticosteroid treatment results in a significant reduction in total symptom score and nasal polyp score in patients with CRSwNP.
- Nasal corticosteroid [1a (-)]: The current evidence does not support the use of nasal corticosteroids for symptomatic relief from the common cold.

Antihistamines (oral and topical)

- Antihistamines [1a]: Antihistamines have a limited short-term (days 1 and 2 of treatment) beneficial effect on severity of overall symptoms in adults but not in the mid to long term. There is no clinically significant effect on nasal obstruction, rhinorrhea, or sneezing.

Anti-leukotrienes

- The EPOS2020 steering group does not advise adding montelukast to nasal corticosteroid but studies evaluating the effect of montelukast in patients that failed nasal corticosteroids are missing.
- **Decongestant** (oral / nasal) [Ia]: the current evidence suggests that multiple doses of decongestants may have a small positive effect on subjective measures of nasal congestion in adults with the common cold. Decongestants do not seem to increase the risk of adverse events in adults in the short term.
- Paracetamol (**Acetaminophen**) [Ia]: Paracetamol may help relieve nasal obstruction and rhinorrhea but does not appear to improve other cold symptoms (including sore throat, malaise, sneezing and cough).
- **NSAIDs** [Ia]: NSAIDs do not significantly reduce the total symptom score, or duration of colds. However, for outcomes related to the analgesic effects of NSAIDs (headache, ear pain and muscle and joint pain) NSAIDs produce significant benefits, and malaise shows a borderline benefit, although throat irritation is not improved. Chills show mixed results. For respiratory symptoms, cough and nasal discharge scores are not improved, but the sneezing score is significantly improved. There is no evidence of increased frequency of adverse effects in the NSAID treatment groups.
- **Antihistamine-decongestant-analgesic combinations** [Ia]: Antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children with common colds. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children.
- **Ipratropium bromide** [Ia]: the existing evidence suggests that ipratropium bromide is likely to be effective in ameliorating rhinorrhea. Ipratropium bromide has no effect on nasal congestion and its use is associated with more side effects compared to placebo or no treatment although these appeared to be well tolerated and self-limiting.

Nasal Irrigation

- Nasal irrigation with isotonic saline or Ringer's lactate is an effective treatment in CRS patients.
- The addition of Xylitol, sodium hyaluronate, and xyloglucan to nasal saline irrigation may have a positive effect.
- Nasal irrigation with saline [Ib]: Nasal saline irrigation possibly has benefits for relieving the symptoms of acute URTIs mainly in children and is considered an option by the EPOS steering group.
- Steam / heated humidified air [1a (-)]: The current evidence does not show any benefits or harms from the use of heated, humidified air delivered for the treatment of the common cold.
- **Probiotics** [Ia]: Probiotics may be more beneficial than placebo for preventing acute URTIs. However, the quality of the evidence was (very) low.
- **Vitamin C** [Ia]: Given the consistent effect of vitamin C on the duration and severity of colds in regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them.
- Vaccines [1b (-)]: There are no conclusive results to support the use of vaccines for preventing the common cold in healthy people. This contrasts with influenza vaccines.
- Exercise [Ia]: Regular, moderate-intensity exercise may influence the prevention of the common cold.
- **Echinacea** [1a (-)]: Echinacea products have not been shown to provide benefits for treating colds, although, there could be a weak benefit from some Echinacea products: the results of individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance.
- **Zinc** [Ia]: Zinc administered as zinc acetate or zinc gluconate lozenges at a dose of ≥ 75 mg/day and taken within 24 hours of onset of symptoms significantly reduces the duration of common cold. For those considering using zinc it is advised to use it at this dose throughout the cold. Regarding prophylactic zinc supplementation, currently no firm recommendation can be made because of insufficient data.
- Herbal medicine (excluding Echinacae) [Ib]: Some herbal medicines like BNO1016, Cineole and Andrographis paniculata SHA-10 extract have significant impact on symptoms of common cold without important adverse events. A formal systematic review is missing.

- **Fusafungine** [Ia]: Fusafungine is an effective treatment of common cold especially when administered early. However, serious allergic reactions involving bronchospasm although rare have occurred after the use of fusafungine. For that reason, the medication is no longer on the market.

Treatment evidence and recommendations for adults with acute post-viral rhinosinusitis

- Antibiotics [1a (-)]: There is no benefit from prescribing antibiotics for post viral ARS in adults. There is no effect on cure or duration of disease and there are more adverse events. Based on the moderate level of evidence and the fact that acute post-viral rhinosinusitis is a self-limiting disease, the EPOS2020 steering group advises against the use of antibiotics for adults in this situation.
- Nasal corticosteroids [1a]: Nasal corticosteroids are effective in reducing total symptom score in adults suffering from acute post-viral rhinosinusitis. However, the effect is small. Nasal corticosteroids have not been shown to influence QOL. Acute post-viral rhinosinusitis is a self-limiting disease. Based on the moderate quality of the evidence and the small effect size the EPOS2020 steering group advises only to prescribe a nasal corticosteroid when reduction of the symptoms of the acute post-viral rhinosinusitis is considered necessary.
- Systemic corticosteroids [1a]: Systemic corticosteroids, with or without antibiotics do not have a positive effect on recovery at 7-14 days. There is a small but significant effect of systemic corticosteroids versus placebo on facial pain at days 4-7 after start of the treatment. There are no studies comparing systemic corticosteroids to nasal corticosteroids. The quality of the evidence is low. Based on the evidence, the numbers needed to treat and the potential harm of systemic corticosteroids, the EPOS2020 steering group advises against the use of systemic corticosteroids in patients suffering from acute post-viral rhinosinusitis
- Decongestant (oral / nasal) [Ib]: Nasal decongestants may be effective in improving mucociliary clearance throughout the acute phase of the disease. No studies have been performed evaluating the effect on resolution or reduction of symptoms of post viral ARS. Based on the absence of clinically relevant data, the EPOS2020 steering group cannot advise on the use of decongestants in acute post-viral rhinosinusitis.
- Nasal irrigation with saline [Ib]: One small study did not find a difference between saline nasal spray versus no treatment. One very small study found a larger effect of high volume versus low volume saline rinsing on purulent rhinorrhea and post-nasal drip. Based on the very low quality of the evidence no strong advice can be given about the use of nasal saline irrigation although

on theoretical grounds saline can be expected to be beneficial rather than harmful.

- Homeopathy [Ib]: We found one study evaluating the effect of homeopathy (sinfrontal) showing a significant reduction of symptoms and radiographic improvement versus placebo. Based on the limited evidence the EPOS2020 steering group cannot give clear advice on the use of homeopathy in acute post-viral rhinosinusitis.
- Herbal medicine [Ib]: Some herbal medicines like BNO1016 tablets and Pelargonium sidoides drops and Myrtol (and other essential oil) capsules have significant impact on symptoms of acute postviral rhinosinusitis without significant adverse events.

Treatment evidence and recommendations for children with acute post-viral rhinosinusitis

- Antibiotics [1a (-)]: The use of antibiotics in children with acute post-viral rhinosinusitis is not associated with greater cure/significant improvement. Based on the moderate level of evidence and the fact that acute post-viral rhinosinusitis is a self-limiting disease, the EPOS2020 steering group advises against the use of antibiotics for children in this situation.
- Nasal corticosteroids [1a]: Nasal corticosteroids seem to be effective in reducing total symptom score in children suffering from acute post-viral rhinosinusitis on top of (ineffective) antibiotics. Acute post viral rhinosinusitis is a self-limiting disease. Based on the very low quality of the evidence the EPOS2020 steering group cannot advise on the use of nasal corticosteroids in children with acute post-viral rhinosinusitis.
- Antihistamines [1b (-)]: There is one study evaluating antihistamines versus placebo in addition to (ineffective) antibiotics in children with post-viral ARS showing no additive effect of antihistamines over the treatment given. Based on the very low quality of the evidence, the EPOS2020 steering group cannot advise on the use of antihistamines in post-viral ARS.
- Bacterial lysates [Ib]: One study has shown benefit in the use of OM-85-BV for shortening the duration of illness.

Treatment evidence and recommendations for adults with acute bacterial rhinosinusitis (ABRS)

- Antibiotics [1a]: Antibiotics are effective in a select group of patients with symptoms and signs suggestive of ABRS. From the limited data available (two studies versus one) it seems that amoxicillin/penicillin (beta-lactams) especially are effective, and moxifloxacin (fluoroquinone) is not. The efficacy of

beta-lactams is evident on day three where patients already experience better symptom improvement and continue with a higher number of cures at completion of treatment. However, careful patient selection for those with ABRS is needed to avoid unnecessary use of antibiotics and side effects.

- Antihistamines [1b (-)]: There is one study evaluating antihistamines versus placebo in adults with allergic rhinitis and ABRS showing no effect. Based on the very low quality of the evidence, the EPOS2020 steering group cannot advise on the use of antihistamines in post-viral ARS and ABRS.
- Nasal irrigation with saline [1b (-)]: One study comparing hypertonic saline nasal spray, isotonic saline nasal spray, and no treatment in addition to antibiotics did not find a difference between the groups. Based on the very low quality of the evidence no advice can be given about the use of nasal saline irrigation.
- Sodium Hyaluronate [Ib]: One study evaluating sodium hyaluronate compared to placebo in a nebulizer ampoule for nasal douching in addition to levofloxacin and prednisone showed significantly fewer symptoms and better smell threshold in the sodium hyaluronate group. Based on the very low quality of the evidence no advice can be given about the use of sodium hyaluronate.

Treatment evidence and recommendations for children with acute bacterial rhinosinusitis (ABRS)

- Antibiotics [1a (-)]: Data on the effect of antibiotics on the cure/improvement of symptoms in ABRS in children are very limited. There are only two studies with limited numbers that do not show a significant difference over placebo but do show a significantly higher percentage of adverse events. Larger trials are needed to explain the difference between adults where antibiotics in ABRS have been shown to be effective and this outcome.
- Mucolytics [1b (-)]: Erdosteine as an adjunct to antibiotic was not more effective than placebo.

Treatment evidence and recommendations for adults with chronic rhinosinusitis

- It is important to emphasize that CRS is a chronic disease and ESS a step in the management that is primarily aimed at creating better conditions for local treatment. After surgery continuous appropriate medical treatment is mandatory. If surgery in combination with appropriate medical treatment fails, additional therapy can be considered. Options are the use of aspirin treatment after aspirin desensitization (ATAD)(107), longer (tapering)

treatment with OCS, long term antibiotics(108) and/or biologicals when indicated.

- Short term antibiotics for CRS [1b (-)]: The EPOS2020 steering group, is uncertain, due to the very low quality of the evidence, whether the use of a short course of antibiotics has an impact on patient outcomes in adults with CRS compared with placebo. Also, due to the very low quality of the evidence, it is uncertain whether the use of a short course of antibiotics has an impact on patient outcomes in adults with acute exacerbations of CRS compared with placebo. Gastrointestinal-related adverse events (diarrhea and anorexia) are frequently reported.
- Short term antibiotics for acute exacerbation of CRS [1b (-)]: The EPOS2020 steering group, is uncertain, due to the very low quality of the evidence, whether the use of a short course of antibiotics has an impact on patient outcomes in adults with acute exacerbations of CRS compared with placebo. Gastrointestinal-related adverse events (diarrhea and anorexia) are frequently reported.
- Long term antibiotics for CRS [1a (-)]: The EPOS2020 steering group, due to the low quality of the evidence, is uncertain whether the use of long-term antibiotics has an impact on patient outcomes in adults with CRS, particularly in the light of potentially increased risks of cardiovascular events for some macrolides. Further studies with larger population sizes are needed and are underway.
- Topical antibiotics [1b (-)]: The EPOS2020 steering group, due to the very low quality of the evidence, is uncertain whether or not the use of topical antibiotic therapy has an impact on patient outcomes in adults with CRS compared with placebo.
- Nasal corticosteroids [1a]: Nasal corticosteroids do not affect intraocular pressure or lens opacity. The EPOS2020 steering group advises to use nasal corticosteroids in patients with CRS. Based on the low to very low quality of the evidence for higher dosages or different delivery methods and the paucity of direct comparisons the steering committee cannot advise in favor of higher dosages or certain delivery methods.
- Corticosteroid-eluting implants 1a the placement of corticosteroid-eluting sinus implants in the ethmoid of patients with recurrent polyposis after sinus surgery has a significant but small (0.3 on a 0-3 scale) impact on nasal obstruction but significantly reduces the need for surgery and reduces nasal polyp score. Based on the moderate to high quality of the evidence the steering group considered the use of corticosteroid-eluting sinus implants in the ethmoid an option.

- Systemic corticosteroids [1a]: A short course of systemic corticosteroid, with or without local corticosteroid treatment results in a significant reduction in total symptom score and nasal polyp score. Although the effect on the nasal polyp score remains significant up to three months after the start of treatment, by that time there is no longer an effect on the symptom score. The EPOS2020 steering group felt that 1-2 courses of systemic corticosteroids per year can be a useful addition to nasal corticosteroid treatment in patients with partially or uncontrolled disease. A short course of systemic corticosteroid postoperatively does not seem to influence quality of life. Systemic corticosteroids can have significant side effects.
- Antihistamines [Ib]: There is one study reporting on the effect of antihistamines in partly allergic patients with CRSwNP. Although there was no difference in total symptom score, the days with a symptom score ≤1 was higher in the treated group. The quality of the evidence comparing antihistamines with placebo was very low. There is insufficient evidence to decide on the effect of the regular use of antihistamines in the treatment of patients with CRS.
- Anti-leukotrienes [1b (-)]: Based on the very low quality of the available evidence, the EPOS2020 steering group is unsure about the potential use of montelukast in CRS and does not recommend its use unless in situations where patients do not tolerate nasal corticosteroids. Also, the quality of the evidence comparing montelukast with nasal corticosteroid is low. Based on the evidence, the steering group does not advise adding montelukast to nasal corticosteroid but studies evaluating the effect of montelukast in patients that failed nasal corticosteroids are missing.
- Decongestant [Ib]: Although the risk of rebound swelling was not shown in this study, the EPOS2020 steering group suggests in general not to use nasal decongestants in CRS. In situations where the nose is very blocked, the temporary addition of a nasal decongestant to nasal corticosteroid treatment can be considered.
- Nasal irrigation with saline [Ia]: the steering group advises the use of nasal saline irrigation with isotonic saline or Ringer's lactate with or without the addition of xylitol, sodium hyaluronate, and/or xyloglucan and advises against the use of baby shampoo and hypertonic saline solutions due to side effects.
- Aspirin treatment after desensitization (ATAD) with oral aspirin in N-ERD [Ia]: Based on these data, the EPOS2020 steering group suggests that ATAD can be a treatment for N-ERD patients with CRSwNP whenever there is confidence in the patient's compliance.

- Aspirin treatment after desensitization (ATAD) with nasal lysine aspirin in N-ERD [1b (-)]: ATAD with lysine aspirin and platelet inhibitors (like Pradugrel) have not been shown to be an effective treatment in CRSwNP patients with N-ERD and are not advised.
- Low salicylate diet [Ib]: Diets, like low salicylate diet have been shown to improve endoscopic scores and may improve symptoms compared to a normal diet in patients with N-ERD. However, the quality of the evidence at this moment is not enough to draw further conclusions.
- Local and systemic antifungal treatments [1a (-)]: Local and systemic antifungal treatments do not have a positive effect of QOL, symptoms and signs of disease in patients with CRS. The EPOS2020 steering group advises against the use of anti-mycotics in CRS.
- Anti-IgE [Ib]: Due to the small study population in the existing studies, further studies with larger population sizes are needed and are underway. The available data is insufficient to advise on the use of anti-IgE in CRSwNP at this moment.
- Anti-Il-5 [Ib]: The EPOS2020 steering group advises use of mepolizumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies (when approved).
- Anti IL-4/IL-13 (IL-4 receptor, The EPOS steering group advises to use dupilumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies.
- Probiotics [1b (-)]: Although probiotic therapies show theoretical promise, the two studies performed so far did not show any differences compared to placebo. For this reason, the EPOS2020 steering group advises against the use of probiotics for the treatment of patients with CRS.
- Muco-active agents [1b]: The EPOS2020 steering group considered the quality of the data insufficient to advise on the use of muco-active agents in the treatment of patients with CRS.
- Herbal treatment [1b]: based on the available data, the EPOS2020 group cannot advise on the use of herbal medicine in CRS.
- Acupuncture and traditional Chinese medicine [1b (-)]: For this reason, the EPOS2020 steering group advises against the use of traditional Chinese medicine or acupuncture.
- Oral verapamil [1b]: Based on the potential side effects the EPOS2020 steering group advises against the use of oral verapamil.

- Nasal furosemide [1b]: The EPOS2020 steering group cannot advise on the use of nasal furosemide.
- Capsaicin [1b]: The quality of the evidence is low, and the EPOS steering group concludes that capsaicin may be an option in treatment of CRS in patients with CRSwNP but that larger studies are needed.
- Proton-pump inhibitors [1b (-)]: The EPOS2020 steering group therefore does advise against the use of proton pump inhibitors in the treatment of CRS.
- Bacterial lysate [1b]: Based on this limited evidence, the EPOS2020 steering group cannot advise on the use of Broncho-Vaxom in the treatment of CRS.
- Phototherapy [1b (-)]: Based on the evidence, the EPOS2020 steering group cannot make a recommendation on the use of phototherapy in patients with CRS.
- Filgrastim (r-met-HuG-CSF) [1b (-)]: Based on the evidence, the EPOS2020 steering group cannot make a recommendation on the use of Filgrastim in patients with CRS.
- Colloidal silver nasal spray [1b (-)]: Based on the evidence, the EPOS2020 steering group cannot make a recommendation on the use of colloidal silver nasal spray in patients with CRS.

Pediatric chronic rhinosinusitis

- Antibiotics [1b (-)]: There is no high-level evidence to support the efficacy of either short- or long-term antibiotics for CRS in children.
- Nasal corticosteroids [5]: There is no evidence regarding the efficacy of intranasal steroids in the treatment of CRS in children. Nevertheless, the EPOS steering group is supportive of their use considering their anti-inflammatory effects and excellent safety record in children.
- Systemic Steroids [1b (+)]: Adding a taper course of systemic steroids to an antibiotic (not effective on its own) is more effective than placebo in the treatment of pediatric CRS. Judicious use of this regimen is advised considering systemic side effects.
- Saline Irrigation [Ib (+)]: There are a few clinical trials demonstrating the efficacy of saline irrigations in pediatric patients with CRS. The EPOS steering group is supportive of the use of saline considering the excellent safety record in children.
- Adenoidectomy [4]: Adenoidectomy is effective in younger children with symptoms of CRS. The EPOS steering group supports adenoidectomy in young children refractory to appropriate medical therapy.

- FESS [4]: FESS is safe and effective for the treatment of older children with CRS refractory to medical therapy or previous adenoidectomy.

Concomitant diseases in chronic rhinosinusitis

- Role of allergy and chronic rhinosinusitis: optimal treatment of allergic rhinitis seems advisable.
- Immunodeficiencies and their role in CRS: the prevalence of secondary immune deficiency is rising due to the increased use of immunosuppressive agents such as rituximab, corticosteroids, and other drugs and otorhinolaryngologists need to directly ask about immunosuppressive agents in their history taking.
- Lower airway disease including asthma in relation to CRS: endoscopic sinus surgery in asthma has been reported to improve multiple clinical asthma parameters with improved overall asthma control, reduced frequency of asthma attacks and number of hospitalizations, as well as decreased use of oral and inhaled corticosteroids.
- Cystic fibrosis (CF): detecting gram-negative sinus bacteria at an early stage is an important step towards eradicating the bacteria and avoiding a chronic bacterial sinus infection. The use of topical antibiotics correlates with improvement in symptom and endoscopic scoring and is safe.
- Primary ciliary dyskinesia (PCD): prolonged macrolide therapy has been shown to produce marked improvement in symptomatology of PCD due to the anti-inflammatory and immune-mediating properties of the antibiotic. Surgical intervention (ESS) may be required when medical therapy has failed.
- Fungal rhinosinusitis: there are three principles for treatment: 1. Systemic antifungals therapy should be started; 2. Patients should undergo, at least, endoscopic surgical debridement of necrotic sinonasal tissue, which may need to be repeated; 3. The patient's immune suppression should be reduced when feasible. The mainstay of treatment remains surgical though may be combined with medical therapies in invasive and allergic forms.
- Vasculitis: systemic steroids remain the mainstay of treatment in sarcoidosis, though hydroxychloroquine, steroid sparing cytotoxic agents such as methotrexate and TNF-alpha antagonists such as infliximab are being used.

CRS treatment during pregnancy

- Expert panel recommendations for rhinosinusitis management during pregnancy included continuing nasal corticosteroid sprays for CRS maintenance, using pregnancy-safe antibiotics for acute rhinosinusitis and

CRS exacerbations, and discontinuing aspirin desensitization for aspirin exacerbated respiratory disease.

Peri-operative and post-operative medications

- The quality of the evidence for the use of commonly administered peri-operative medication such as (nasal) corticosteroids and antibiotics is low, mainly due to insufficient and small studies.
- The use of peri-operative corticosteroids reduces blood loss and operation time and improves the quality of the surgical field. There is also high-quality evidence that long term use of nasal corticosteroids is effective and safe for treating patients with CRS with significant impact on nasal symptoms and quality of life improvement. Nasal corticosteroids reduce nasal polyp size and when administered after endoscopic sinus surgery, nasal corticosteroids prevent polyp recurrence.
- Although the quality of direct evidence postoperatively is missing, the EPOS2020 steering committee recommends using nasal corticosteroids postoperatively. Based on the low positive evidence and the excellent safety profile the group also recommends using nasal saline irrigation with isotonic saline or Ringer's lactate, potentially with the addition of sodium hyaluronate, and advise against the use of baby shampoo and hypertonic saline solutions due to side effects in the postoperative period after FESS. Otherwise, based on the low-quality evidence, the steering group cannot recommend the use of peri-operative antibiotics. The group also advises against the use of anti-mycotics.

1.2.2 American Academy of Allergy, Asthma & Immunology (AAAAI) Joint Task Force on Practice Parameters GRADE Guidelines for the Medical Management of Chronic Rhinosinusitis with Nasal Polyposis [2023]

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[8].

Table 5. Grades of Recommendations and Interpretations

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 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 (i.e., 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.

Question 1: Should INCS (topical corticosteroid), rather than no INCS, be used in CRSwNP (Chronic rhinosinusitis without nasal polyps)?

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

Factors driving recommendation type: The small-to-moderate treatment effect and low certainty evidence when all 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).

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 symptoms for which the improvement was important while receiving treatments other than biologics (i.e., 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 NMA linked to this guideline.
- Patients who value not having the burden of payment and insurance approvals may be less likely to choose biologics. d 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 (e.g., asthma) may be a reason to choose biologics in general and even specific biologics.

Question 3: Should ATAD (Aspirin therapy after desensitization), rather than no ATAD, be used in people with AERD (Aspirin (nonsteroidal anti-inflammatory)-exacerbated respiratory disease)?

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

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' intolerance to NSAIDs and who require an NSAID for alternative indications (e.g., cardiovascular disease) may prefer ATAD over other options.

1.2.3 American College of Allergy, Asthma & Immunology Chronic Rhinosinusitis Practice Parameter [2022]

The Allergy-Immunology Joint Task Force on Practice Parameters has published the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines for the medical management of chronic rhinosinusitis with nasal polyposis (CRSwNP). The practice parameter provides evidence-based guidelines on the use of intranasal corticosteroids (INCS) and biologics for CRSwNP, and aspirin therapy after desensitization (ATAD) for the management of aspirin-exacerbated respiratory disease (AERD). Evidence on surgery was not assessed. Overall, the guidelines suggest INCS rather than no INCS (conditional recommendation, low certainty of evidence), biologics rather than no biologics (conditional recommendation, moderate certainty of evidence), and ATAD rather than no ATAD (conditional recommendation, moderate certainty of evidence)[9].

The quality of the evidence was assessed for each outcome of interest after the GRADE approach. The certainty of the evidence was categorized into very low, low, moderate, or high based on the following domains: risk of bias, imprecision, inconsistency, publication bias, presence of large effects, dose-effect relationship, and confounding. T*he practice parameter labeled recommendations as "strong" or "conditional" according to the GRADE approach. For strong recommendations, the words "the guideline panel recommends" are used, and for conditional recommendations, the words "the guideline panel suggests" are used.*

- The chronic rhinosinusitis with nasal polyps (CRSwNP) practice parameter focuses on evidence-based guidance on intranasal (topical) corticosteroids (INCS), biologics, and aspirin therapy after desensitization (ATAD).
- The guideline panel suggested INCS rather than no INCS in patients with CRSwNP, and that patient-important outcomes differ by delivery method.

- The guideline panel suggested biologics rather than no biologics in patients with CRSwNP, and among biologics, **dupilumab** and **omalizumab** are among the most effective.
- The guideline panel suggested ATAD rather than no ATAD in patients with AERD; however, between a biologic and ATAD, a biologic is likely to be safer and more effective.

Table 6. Summary of Recommendations

Management	Condition	Recommendation (vs. no treatment)	GRADE	Considerations for shared decision making
INCS	CRSwNP	Yes	Conditional, low certainty of evidence	Delivery method (stent, spray, EDS are the most beneficial) and associated cost, availability, accessibility; small treatment effect sizes
Biologics	CRSwNP	Yes	Conditional, moderate certainty of evidence	Symptom response to treatment other than biologics; disease burden at presentation (may be preferred as initial treatment if high disease burden); variability in efficacy among biologics; payment and insurance issues
ATAD	AERD	Yes	Conditional, moderate certainty of evidence	Adverse effects (gastrointestinal bleeding); risk of desensitization in poorly controlled asthma

Abbreviations: ATAD, aspirin therapy after desensitization; AERD, aspirin-exacerbated respiratory disease; EDS, exhalation delivery system; CRSwNP, chronic rhinosinusitis with nasal polyps; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; INCS, intranasal corticosteroids.

1.2.4 Korean Society of Otorhinolaryngology-Head and Neck Surgery and Korean Rhinologic Society Clinical Practice Guideline: Nasal Irrigation for Chronic Rhinosinusitis in Adults [2022]

The Korean Society of Otorhinolaryngology-Head and Neck Surgery and Korean Rhinologic Society appointed a guideline development group (GDG) to establish a

clinical practice guideline, and the GDG developed a guideline for nasal irrigation for adult patients with chronic rhinosinusitis (CRS). The guideline focuses on knowledge gaps, practice variations, and clinical concerns associated with nasal irrigation. Nasal irrigation has been recommended as the first-line treatment for CRS in various guidelines, and its clinical effectiveness has been demonstrated through several studies with robust evidence[10].

Table 7. Evidence Levels and Grades of Recommendations

Level of Evidence			
High-quality evidence		RCTs without important limitations or overwhelming evidence from observational studies	
Medium-quality evidence		RCTs without important limitations or overwhelming evidence from observational studies	
Low-quality evidence		Observational studies/case studies/expert opinion	
Aggregate grades of evidence by question type			
Grade	**OCEBM Level**	**Treatment**	**Harm**
A	1	Systematic review of randomized trials	Systematic review of randomized trials, nested case-control studies, or observational studies with dramatic effect
B	2	Randomized trials or observational studies with dramatic effects or highly consistent evidence	Randomized trials or observational studies with dramatic effects or highly consistent evidence
C	3-4	Nonrandomized or historically controlled studies, including case-control and observational studies	Nonrandomized controlled cohort or follow-up study (post-marketing surveillance) with sufficient numbers to rule out a common harm, case-series, case-control, or historically controlled studies

D	5	Case reports, mechanism-based reasoning, or reasoning from first principles
X	N/A	Case reports, mechanism-based reasoning, or reasoning from first principles

OCEBM, Oxford Centre for Evidence-Based Medicine; NA, not applicable

Guideline definitions for evidence-based statements

Statement	Definition	Implied Obligation
Strong recommendation	A strong recommendation means that the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B). In some clearly identified circumstances, strong recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain, and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation means that the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C). In some clearly identified circumstances, recommendations may be made on the basis of lesser	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.

	evidence when high-quality evidence is impossible to obtain, and the anticipated benefits outweigh the harms	
Option	An option means that either the quality of evidence that exists is suspect (grade D) or those well-done studies (grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decisionmaking regarding appropriate practice, although they may set bounds on alternatives. Patient preference should have a substantial influencing role

1. Nasal saline irrigation: Clinicians should recommend nasal saline irrigation to patients with chronic sinusitis or those who have undergone endoscopic sinus surgery. Strong recommendation
2. Saline tonicity: Clinicians may recommend using isotonic saline as a nasal irrigation solution for patients considering cost, convenience, and safety. However, it is unclear whether there is a clear difference in the therapeutic effect of hypertonic and isotonic saline solutions. Option
3. Saline temperature: Clinicians may recommend using room-temperature saline (around 20°C) as a nasal irrigation solution for patients considering effectiveness and convenience. If the patient prefers, then it is also completely acceptable to use a saline solution heated to 40°C. However, it is not recommended to immediately use a solution that has been refrigerated or to use a hot solution that exceeds 40°C for safety reasons. Option
4. Steroid solution: Clinicians may recommend nasal irrigation with solutions containing steroids to patients with chronic rhinosinusitis who have undergone endoscopic sinus surgery. Option
5. Antibiotic solution: Clinicians should not routinely recommend nasal irrigation with solutions containing antibiotics for the management of patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. Recommendation against
6. Antifungal solution: Clinicians should not routinely recommend nasal irrigation with solutions containing antifungal agents for the management of patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. Recommendation against

7. Miscellaneous solution–hyaluronate: Clinicians may recommend nasal irrigation with solutions containing sodium hyaluronate to patients with chronic rhinosinusitis. Option

   Miscellaneous solution–xylitol: Clinicians may recommend nasal irrigation with solutions containing xylitol to patient's post-endoscopic sinus surgery. Option

   Miscellaneous solution–honey: Clinicians should not routinely recommend nasal irrigation with solutions containing honey for the management of patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. Recommendation against

8. Irrigation solution preparation: Clinicians should recommend an appropriate irrigation fluid preparation method for patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. For irrigation fluid, bottled or distilled water should preferably be used. If tap water is used, boil it for at least 5 minutes and cool before use or expose it to ultraviolet light for at least 45 seconds. Recommendation
9. Equipment Clinicians should recommend nasal irrigation performed by high-volume with low- or high-pressure delivery rather than low-volume with low- or high-pressure delivery in patients with chronic rhinosinusitis. Recommendation
10. Disinfection: Clinicians should recommend the following techniques for appropriate irrigation equipment care to patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. Irrigation equipment (according to the equipment material and manufacturer's recommendations, if possible) should be boiled (for more than 2 minutes) or microwaved for 1 minute and 30 seconds regularly before and after use. Recommendation
11. Posture Clinicians may recommend the head down-and-forward position as being better for high-volume nasal irrigation, whereas the nose-to-ceiling position is more effective at delivering low-volume nasal irrigation. Option

1.2.5 British Rhinological Society (BRS) Consensus Guidance on the Use of Biological Therapies for Chronic Rhinosinusitis with Nasal Polyps [2021]

These guidelines were created based on current evidence and relative risks of adverse effects and the costs of different treatments, which reflect the views of the British Rhinological Society (BRS) Council on where the use of biologics should be positioned within treatment pathways for CRSwNP, specifically in the setting of the National Health Service (NHS)[11].

The RAND/UCLA methodology with a multi-step process was used; using a 9-point Likert scale, for each indication, the panelists scored whether a treatment was either:

- Not recommended/inappropriate; should not be prescribed for the indication described within the NHS, based on current evidence base and costs (scored 1-3)
- Uncertain; (scored 4-6)
- Recommended/appropriate; should be prescribed for the indication described within the NHS, based on current evidence base and costs (scored 7-9)

The following statements summarize all situations where agreement was reached that it is appropriate that biologics be considered in the treatment of CRSwNP within the NHS at the current time.

Biologics SHOULD be considered if the following conditions are met.

- Patient with CRS with nasal polyps AND moderate symptom severity or more (SNOT22 ≥ 21 or VAS ≥ 4) AND Lund-Mackay CT Score ≥ 8

  AND a score of 5 points or more out of a possible 7

  Number of courses of OCS (Oral corticosteroids) in last 12 months (to max of 2 points)

  1 course in last 12 months = 1 point

  2 or more courses in last 12 months = 2 points

  Unable to take OCS due to medical contraindicators = 2 points

  Number of previous surgeries for CRSwNP (to max of 3 points)

  1 previous sinus surgery = 1 point

  2 previous sinus surgeries = 2 points

  3 or more previous sinus surgeries = 3 points

  If unfit for surgery = 3 points

  Comorbid asthma = 1 point

  Comorbid N-ERD = 1 point in addition to 1 point for co-morbid asthma

1.2.6 Canadian Multidisciplinary Expert Consensus on the Use of Biologics in Upper Airways: A Delphi Study [2023]

This white paper considers the perspectives of experts in various disciplines such as rhinology, allergy, and respirology across Canada, all of whom have unique and

valuable insights to contribute on how to best approach patients with upper airway disease from a multidisciplinary perspective[12].

Patient population

- Patients with chronic symptoms of upper airway disease which include facial pressure/pain, nasal obstruction/congestion, nasal discharge, or a loss of smell should be evaluated for upper airway disease. Recommendation
- Patients treated appropriately for asthma with persistent chronic upper airway symptoms should be referred for further evaluation of upper airway disease. Recommendation
- All CRSwNP patients with lower respiratory symptoms who have not previously been evaluated for asthma should be evaluated for possible asthma and referred to a clinician who can provide a systematic evaluation. Recommendation
- Clinician(s) evaluating for upper airway disease should evaluate the nose with nasal endoscopy or in communities where no nasal endoscopy is available, anterior rhinoscopy is acceptable when the diagnosis of nasal polyps is apparent. If nasal endoscopy is unremarkable or unavailable, a CT scan could be ordered to rule out sinus disease without polyps. Recommendation
- CT reports indicating polyps are not sufficient to make the diagnosis of CRSwNP and starting on biologics. Recommendation
- All endotypes of CRSwNP confirmed by endoscopy or anterior rhinoscopy are considered eligible for a trial of biologic therapy. Recommendation
- Biologics should be principally considered for those who have undergone adequate sinus surgery within the past 5 years and are refractory to oral and nasal steroids. Patients unsuitable for surgery who have failed medical therapy may also be considered candidates for biologic therapy based on shared patient decision making. Recommendation
- The adequacy of previous surgery matters in determining if subsequent surgical management is required versus initiation of biologic therapy. This could be evaluated with a CT scan and/or endoscopy to determine if each of the diseased sinus cavities can receive appropriate topical drug delivery. Recommendation
- Patients with refractory CRSwNP after surgery should be counselled regarding their options which include revision sinus surgery or biologics. Referral to a specialist that can counsel and/or perform extended surgical procedures should be sought if available. Recommendation

- Patients with CRSwNP do not need co-existing Type 2 inflammatory condition such as asthma to be considered for biologic therapy. Recommendation
- For most patients, CRSwNP symptoms need to be severe based on the clinician's choice of a validated patient reported outcome measure (PROM) for chronic sinus disease to warrant the use of biologics. There is a subgroup of patients that may score lower than severe disease on a PROM due to acclimatization to their symptoms (i.e., allergic fungal rhinosinusitis and chronic prednisone users) and these cases should be considered for biologics based on shared decision making. Recommendation.
- In patients with CRSwNP and coexisting asthma, who qualify for a biologic therapy based on upper airway indications, a consultation with a specialist experienced in managing asthma is recommended before choosing the most appropriate biologic. Recommendation
- There is insufficient evidence to make a recommendation for providing biologics to patients with CRSsNP Recommendation.
- Where possible, patients with Aspirin Exacerbated Respiratory Disease (AERD) should be preferentially managed by a multidisciplinary team. Recommendation

Biological Markers

- At the time of writing, there are no biological markers required to start CRSwNP patients on biologics nor any markers to indicate best biologic to use. Option

Biological Response

- Nasal response to biologics should be assessed by 16 weeks after initiating biologic therapy with subjective and objective measures. If these improvements are not met at 16 weeks, the biology should be re-evaluated. Recommendation
- Patients should be evaluated every 6 months in the first two years of biologic initiation and yearly thereafter Recommendation.
- When treating co-existing CRSwNP and asthma, an attempt should be made to obtain optimal results with a single biologic in both diseases. Recommendation
- Pre-biologic criteria may be used to qualify apatient for a second or subsequent biologic therapy in case of sub-optimal response to the first biologic. Recommendation

- CRSwNP who have exhausted biologics and not achieved simultaneous adequate response in both the upper and lower airways could be evaluated for possible revision sinus surgery. Recommendation

Safety Profile

- The risk of side effects is low in the short-term use of biologics in CRSwNP Recommendation

Cost of Biologics

- Cost and access to biologics should be considered in the decision making of the use of biologics Recommendation.

Section 2.0 Drug Therapy in Sinusitis

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

After November 2019, new drugs for the management of sinusitis have received FDA or EMA approval. In fact, monoclonal antibodies; **Omalizumab and Dupilumab,** were registered by the SFDA. Hence, relevant information pertaining to this drug can be found below.

2.1.1 Omalizumab

This section includes pertinent information regarding the use of ***Omalizumab in*** Sinusitis[13].

Table 8. Omalizumab Drug Information

SCIENTIFIC NAME Omalizumab	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes

PMDA	Yes
Indication (ICD-10)	J32
Drug Class	Monoclonal Antibody
Drug Sub-class	Anti-Asthmatic
ATC Code	R03DX05
Pharmacological Class (ASHP)	Monoclonal Antibody
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled syringe
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	**Rhinosinusitis (chronic) with nasal polyps: SUBQ:** Dose and frequency based on **actual body weight** and **pretreatment** total IgE serum levels. Dosing should be adjusted during therapy for significant changes in actual body weight. Dosing should **not** be adjusted based on total IgE levels taken during treatment or <1 year following interruption of therapy. If therapy has been interrupted for ≥1 year, total IgE levels may be reevaluated for dosage determination.

Pretreatment serum IgE	Actual body weight (kg)	Dose (mg) SUBQ	Frequency (weeks)
≥30 to 100 units/mL	30 to 40 kg	75 mg	Every 4 weeks
	>40 to 90 kg	150 mg	
	>90 to 150 kg	300 mg	
>100 to 200 units/mL	30 to 40 kg	150 mg	Every 4 weeks
	>40 to 90 kg	300 mg	
	>90 to 125 kg	450 mg	
	>125 to 150 kg	600 mg	
>200 to 300 units/mL	30 to 40 kg	225 mg	Every 4 weeks
	>40 to 60 kg	300 mg	
	>60 to 90 kg	450 mg	
	>90 to 125 kg	600 mg	
	>125 to 150 kg	375 mg	Every 2 weeks
>300 to 400 units/mL	30 to 40 kg	300 mg	Every 4 weeks
	>40 to 70 kg	450 mg	
	>70 to 90 kg	600 mg	
	>90 to 125 kg	450 mg	Every 2 weeks
	>125 to 150 kg	525 mg	
>400 to 500 units/mL	30 to 50 kg	450 mg	Every 4 weeks
	>50 to 70 kg	600 mg	
	>70 to 90 kg	375 mg	Every 2 weeks
	>90 to 125 kg	525 mg	
	>125 to 150 kg	600 mg	
>500 to 600 units/mL	30 to 40 kg	450 mg	Every 4 weeks
	>40 to 60 kg	600 mg	
	>60 to 70 kg	375 mg	Every 2 weeks
	>70 to 90 kg	450 mg	
	>90 to 125 kg	600 mg	
	>125 kg	Use not recommended.	
>600 to 700 units/mL	30 to 40 kg	450 mg	Every 4 weeks
	>40 to 50 kg	600 mg	
	>50 to 60 kg	375 mg	Every 2 weeks
	>60 to 80 kg	450 mg	
	>80 to 90 kg	525 mg	
	>90 kg	Use not recommended.	

>700 to 800 units/mL	30 to 40 kg	300 mg	Every 2 weeks
	>40 to 50 kg	375 mg	
	>50 to 70 kg	450 mg	
	>70 to 80 kg	525 mg	
	>80 to 90 kg	600 mg	
	>90 kg	Use not recommended.	
>800 to 900 units/mL	30 to 40 kg	300 mg	Every 2 weeks
	>40 to 50 kg	375 mg	
	>50 to 60 kg	450 mg	
	>60 to 70 kg	525 mg	
	>70 to 80 kg	600 mg	
	>80 kg	Use not recommended.	
>900 to 1,000 units/mL	30 to 40 kg	375 mg	Every 2 weeks
	>40 to 50 kg	450 mg	
	>50 to 60 kg	525 mg	
	>60 to 70 kg	600 mg	
	>70 kg	Use not recommended.	
>1,000 to 1,100 units/mL	30 to 40 kg	375 mg	Every 2 weeks
	>40 to 50 kg	450 mg	
	>50 to 60 kg	600 mg	
	>60 kg	Use not recommended.	
>1,100 to 1,200 units/mL	30 to 40 kg	450 mg	Every 2 weeks
	>40 to 50 kg	525 mg	
	>50 to 60 kg	600 mg	
	>60 kg	Use not recommended.	
>1,200 to 1,300 units/mL	30 to 40 kg	450 mg	Every 2 weeks
	>40 to 50 kg	525 mg	
	>50 kg	Use not recommended.	
>1,300 to 1,500 units/mL	30 to 40 kg	525 mg	Every 2 weeks
	>40 to 50 kg	600 mg	
	>50 kg	Use not recommended.	

Maximum Daily Dose Adults*	**600 mg**
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Dosing: Altered Kidney Function: Adult**

	There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Adjustment for Toxicity: Adult** Severe hypersensitivity reaction or anaphylaxis: Discontinue treatment. Fever, arthralgia, and rash: Discontinue treatment if this constellation of symptoms occurs.
Prescribing edits*	AGE, CU, QL, MD, PA, ST
AGE (Age Edit): Not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.	
CU (Concurrent Use Edit): Add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adults with inadequate response to nasal corticosteroids.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Prescribed by or in consultation with an allergist/immunologist, otolaryngologist, or pulmonologist	
PA (Prior Authorization): Omalizumab should be given as add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adults with inadequate response to nasal corticosteroids at a dose and frequency based on actual weight and pretreatment total IgE serum levels at a maximum dose of 600 mg every 4 weeks. Omalizumab should be prescribed by or in consultation with an allergist/immunologist, otolaryngologist, or pulmonologist.	
QL (Quantity Limit 600 mg every 4 weeks	
ST (Step Therapy): Treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) when medicines to treat CRSwNP called nasal corticosteroids have not worked well enough.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** • Local: Injection-site reaction (asthma: 45%, severe 12%; chronic spontaneous urticaria and chronic rhinosinusitis with nasal polyps: 3% to 5%; may include bleeding at

	injection site, bruising at injection site, burning sensation at injection site, erythema at injection site, induration at injection site, injection-site pruritus, pain at injection site, residual mass at injection site, swelling at injection site, urticaria at injection site, warm sensation at injection site) • Nervous system: Headache (children: ≥3%; adolescents and adults: 6% to 12%) **Most serious:** • Cardiovascular effects • Eosinophilia and vasculitis • Fever/arthralgia/rash • Hypersensitivity/anaphylactoid reactions • Malignant neoplasms
Drug Interactions	**Category X** Loxapine *Depends on Route* **Category C** CEfgartigimod Alfa CRozanolixizumab
Special Population	**Reproductive Considerations** Data related to the use of monoclonal antibodies for the treatment of asthma in pregnancy are limited. The long half-life of monoclonal antibodies should be considered when prescribing to patients planning to become pregnant.
Pregnancy	Omalizumab crosses the placenta.
Lactation	Omalizumab crosses the placenta.
Contraindications	Severe hypersensitivity reaction to omalizumab or any component of the formulation
Monitoring Requirements	Anaphylactic/hypersensitivity reactions (observe patients for 2 hours after the first 3 injections and 30 minutes after subsequent injections [Lieberman 2015]

	or in accordance with individual institution policies and procedures); baseline serum total IgE; FEV_1, peak flow, and/or other pulmonary function tests; monitor for signs of infection.
Precautions	***Disease-related concerns:*** Asthma: Therapy has not been shown to alleviate acute asthma exacerbations; do not use to treat acute bronchospasm, status asthmaticus, or other allergic conditions. Parasitic infections: Use with caution and monitor patients at high risk for parasitic (helminth) infections; risk of infection may be increased; appropriate duration of continued monitoring following therapy discontinuation has not been established. ***Concurrent drug therapy issues:*** Corticosteroid therapy: Do not discontinue corticosteroids abruptly following initiation of omalizumab therapy. Reductions in corticosteroid dose should be gradual, if appropriate. Clinicians should note that a reduction in corticosteroid dose may be associated with withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. The combined use of omalizumab and corticosteroids in patients with chronic spontaneous urticaria has not been evaluated. ***Dosage forms specific issues:*** Latex: Prefilled syringe: The needle cap may contain natural rubber latex.
Black Box Warning	Anaphylaxis: presenting bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue,

	has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as after the first dose of omalizumab but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, initiate omalizumab therapy in a health care setting and closely observe patients for an appropriate period of time after omalizumab administration. Health care providers administering omalizumab should be prepared to manage anaphylaxis, which can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care if symptoms occur. Selection of patients for self-administration of omalizumab should be based on criteria to mitigate risk from anaphylaxis.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sinusitis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 9. Omalizumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Omalizumab	NICE[14]	**February 2021:** NICE is unable to make a recommendation on omalizumab (Xolair) for treating chronic rhinosinusitis with nasal polyps in adults because Novartis Pharmaceuticals did not provide an evidence submission.

	CADTH[15]	**October 2023**: CADTH is unable to recommend reimbursement as a submission was not filed by the manufacturer
	HAS[16]	N/A
	IQWIG[17]	N/A
	PBS[18]	N/A

Conclusion Statement – Omalizumab

No HTA recommendations about the use of Omalizumab in patients with Sinusitis Recommendations are for the use of Omalizumab in patients with other medical conditions.

2.1.2 Dupilumab

This section includes pertinent information regarding the use of ***Dupilumab*** *in* Sinusitis[13].

Table 10. Dupilumab Drug Information

SCIENTIFIC NAME Dupilumab	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	J32
Drug Class	Interleukin-4 Receptor Antagonist
Drug Sub-class	Monoclonal Antibody
ATC Code	R03DX05
Pharmacological Class (ASHP)	Monoclonal Antibody
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	SUBQ: 300 mg once every other week.
Maximum Daily Dose Adults*	**600 mg**
Dose (pediatrics)	N/A

Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Dosing: Altered Kidney Function: Adult** There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	**AGE, CU, MD, ST, PA**
AGE (Age Edit): Safety and effectiveness in pediatric patients younger than 18 years of age with CRSwNP have not been established.	
CU (Concurrent Use Edit): Add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adults with inadequate response to nasal corticosteroids.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Prescribed by or in consultation with an allergist/immunologist, otolaryngologist, or pulmonologist	
PA (Prior Authorization): Dupilumab should be given as add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adults with inadequate response to nasal corticosteroids at a dose of 300 mg once every other week. Dupilumab should be prescribed by or in consultation with an allergist/immunologist, otolaryngologist, or pulmonologist.	
QL (Quantity Limit N/A	
ST (Step Therapy): Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** • Immunologic: Antibody development (1% to 16%; neutralizing: 2% to 5%) • Local: Injection-site reaction (6% to 38%) • Respiratory: Upper respiratory tract infection (18%) **Most serious:** • Dermatologic reactions

	• Ocular effects
Drug Interactions	**Category X** XAdenovirus (Types 4, 7) Vaccine XBCG Vaccine (Immunization) XCholera Vaccine XDengue Tetravalent Vaccine (Live) XEbola Zaire Vaccine (Live) XInfluenza Virus Vaccine (Live/Attenuated) XJapanese Encephalitis Virus Vaccine (Live/Attenuated) XMeasles, Mumps, and Rubella Virus Vaccine XMeasles, Mumps, Rubella, and Varicella Virus Vaccine XMumps Virus Vaccine XPoliovirus Vaccine (Live/Bivalent/Oral) XPoliovirus Vaccine (Live/Trivalent/Oral) XRotavirus Vaccine XSmallpox Vaccine Live XTyphoid Vaccine XVaricella Virus Vaccine XYellow Fever Vaccine XZoster Vaccine (Live/Attenuated) **Categories B and C** CEfgartigimod Alfa CRozanolixizumab BMetoprolol
Special Population	**Reproductive Considerations** Outcome data following use of dupilumab in patients planning a pregnancy are limited. The long half-life of monoclonal antibodies should be considered when treating patients planning to become pregnant.
Pregnancy	Dupilumab is a humanized monoclonal antibody (IgG4). Human IgG crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of

	organogenesis and the highest during the third trimester. Outcome data following use of dupilumab in pregnant patients are limited primarily to case reports
Lactation	It is not known if dupilumab is present in breast milk
Contraindications	Known hypersensitivity to dupilumab or any component of the formulation
Monitoring Requirements	Monitor for signs/symptoms of arthralgia, hypersensitivity reactions, and ocular adverse effects (consider eye exam in patients with unresolved conjunctivitis); signs of infection; exacerbations, symptom control, and pulmonary function tests (eg, FEV_1) in patients treated for asthma; consider rheumatological evaluation in patients with signs of arthralgia.
Precautions	***Concerns related to adverse effects:*** Arthralgia: Arthralgia, including gait disturbances or decreased mobility associated with joint symptoms, has been reported, sometimes requiring hospitalization. May occur within days to months following initiation of therapy and has resolved with or without therapy discontinuation; report new-onset or worsening joint symptoms to health care provider. Eosinophilia and vasculitis: In rare cases, patients may present with serious systemic eosinophilia, sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, a condition which is often treated with systemic corticosteroid therapy. Monitor for eosinophilia, vasculitic rash, worsening pulmonary symptoms,

	cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. A causal association between dupilumab and these underlying conditions has not been established. ***Concurrent drug therapy issues:*** Corticosteroid therapy: Do not discontinue corticosteroids abruptly following initiation of dupilumab therapy. Reductions in corticosteroid dose should be gradual, if appropriate. Clinicians should note that a reduction in corticosteroid dose may be associated with withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. ***Other warnings/precautions:*** Immunogenicity: Dupilumab antibodies, including neutralizing antibodies, may develop; may be associated with lower serum dupilumab concentrations. Vaccines: Patients should be up to date with all immunizations before initiating therapy. Avoid the use of live vaccines in patients treated with dupilumab.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sinusitis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 11. Dupilumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Dupilumab	NICE[14]	**September 20, 2020,** NICE is unable to make a recommendation on dupilumab (Dupixent) for treating chronic rhinosinusitis with nasal polyps because Sanofi did not provide an evidence submission
	CADTH[15]	N/A
	HAS[16]	**October 2020: Favorable opinion for reimbursement** as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyps (CRSwNP) for whom therapy with systemic corticosteroids and surgery do not provide adequate disease control.
	IQWIG[17]	N/A
	PBS[18]	N/A

Conclusion Statement – Dupilumab

Only one favorable opinion by HAS about the use of Dupilumab in patients with Sinusitis.

2.2 Modifications

No modifications have been made since November 2019.

2.3 Delisting

The medications below are no longer SFDA registered[19], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI Sinusitis original clinical guidance.*

- AMOXICILLIN, CLAVULANIC ACID 125,31.25 mg, mg ORAL SUSPENSION
- AMOXICILLIN, CLAVULANIC ACID 250,62.5 mg ORAL SUSPENSION
- CLAVULANIC ACID 62.5 mg, Powder for oral suspension
- PARACETAMOL 500 mg, Capsule

Section 3.0 Key Recommendations Synthesis

Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)

- *Establishing the Diagnosis of CRS*

  An algorithm can be used to diagnose CRS. Aside from the presence of 2 cardinal symptoms for ≥12 weeks, the addition of 1 objective finding on CT or nasal endoscopy greatly increases diagnostic accuracy. Policy Level: Recommendation.[6]

- *Using Imaging to Diagnose CRS*

  CT scanning is recommended for all patients meeting symptom-based criteria for CRS with a lack of objective clinical findings on anterior rhinoscopy or nasal endoscopy, or for preoperative planning. It is an option for confirming CRS instead of nasal endoscopy. Policy Level: Recommendation[6]

- Management: Saline nasal irrigation improves symptoms, QoL and nasal endoscopy for patients with CRSsNP. Duration of treatment should be greater than 8 weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated saline (40◦c) over room temperature saline. Devices with volume greater than 60 mL bring greater benefits. Policy Level: Recommendation[6]

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

- Nebulized saline (5 mL) treatment is an option for treating CRSwNP, particularly patients with thick mucus. Policy Level: Option[6]
- Intranasal Corticosteroids (Standard Delivery) for CRSwNP: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing or additional short-term corticosteroid drop if initial treatment effect is small. Policy Level: INCS: Strong Recommendation. Twice Daily Dosing: Option. High concentration/dose: No recommendation due to mixed and insufficient evidence.[6]
- Oral Corticosteroids: Strong recommendation for the use of oral corticosteroids in the short-term management of CRSwNP. Longer term use of steroids for CRSwNP is not supported by the literature and carries an increased risk of harm to the patient. Policy Level: Strong recommendation for short-term use[6]
- Macrolide Antibiotics: In CRSwNP, macrolides may be beneficial, especially in neutrophil-dominant polyps or in those who are unresponsive to corticosteroids. Policy Level: Option.[6]

- Biologic Therapy:

  Dupilumab: Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options. Policy Level: Recommendation for dupilumab in patients with severe CRSwNP.[6]

  Omalizumab: Consider for severe CRSwNP with concomitant poorly controlled allergic asthma. Policy Level: Option to weak recommendation for patients with severe CRSwNP who have not improved despite other medical and surgical treatments. Weaker recommendation is based on limited body of evidence and high cost. [6]

- Aspirin Desensitization for AERD: Aspirin desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence. Policy Level: Recommendation[6]

- Biologics should be principally considered for those who have undergone adequate sinus surgery within the past 5 years and are refractory to oral and nasal steroids. Patients unsuitable for surgery who have failed medical therapy may also be considered candidates for biologic therapy based on shared patient decision making. Recommendation[12]

AFRS (Allergic Fungal Rhinosinusitis) Management

- Antifungal Therapy: Can consider topical or oral antifungals in AFRS patients recalcitrant to maximal topical steroid therapy and immunotherapy. Policy Level: Option[6]

- Immunotherapy: Immunotherapy remains a reasonable treatment option. Policy Level: Option.[6]

- Anti-IgE: Consider use in difficult to treat AFRS patients with persistent thick mucoid and inflammatory discharge despite topical steroid therapy. Policy Level: Option[6]

Nasal saline irrigation: Clinicians should recommend nasal saline irrigation to patients with chronic sinusitis or those who have undergone endoscopic sinus surgery. Strong Recommendation.[10]

Irrigation solution preparation: Clinicians should recommend an appropriate irrigation fluid preparation method for patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. For irrigation fluid, bottled or distilled water should preferably be used. If tap water is used, boil it for at least 5 minutes and cool before use or expose it to ultraviolet light for at least 45 seconds. Recommendation[10]

Equipment Clinicians should recommend nasal irrigation performed by high-volume with low- or high-pressure delivery rather than low-volume with low- or high-pressure delivery in patients with chronic rhinosinusitis. Recommendation[10]

Disinfection: Clinicians should recommend the following techniques for appropriate irrigation equipment care to patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. Irrigation equipment (according to the equipment material and manufacturer's recommendations, if possible) should be boiled (for more than 2 minutes) or microwaved for 1 minute and 30 seconds regularly before and after use. Recommendation[10]

Treatment evidence and recommendations for adults with acute post-viral rhinosinusitis

- Nasal corticosteroids [1a]: Nasal corticosteroids are effective in reducing total symptom score in adults suffering from acute post-viral rhinosinusitis. However, the effect is small. Nasal corticosteroids have not been shown to influence QOL. Acute post-viral rhinosinusitis is a self-limiting disease. Based on the moderate quality of the evidence and the small effect size the EPOS2020 steering group advises only to prescribe a nasal corticosteroid when reduction of the symptoms of the acute post-viral rhinosinusitis is considered necessary.[7]

Treatment evidence and recommendations for adults with chronic rhinosinusitis

- Systemic corticosteroids [1a]: A short course of systemic corticosteroid, with or without local corticosteroid treatment results in a significant reduction in total symptom score and nasal polyp score. Although the effect on the nasal polyp score remains significant up to three months after the start of treatment, by that time there is no longer an effect on the symptom score. The EPOS2020 steering group felt that 1-2 courses of systemic corticosteroids per year can be a useful addition to nasal corticosteroid treatment in patients with partially or uncontrolled disease. A short course of systemic corticosteroid postoperatively does not seem to influence quality of life. Systemic corticosteroids can have significant side effects.[7]

Treatment evidence and recommendations for adults with acute bacterial rhinosinusitis (ABRS)

- Antibiotics [1a]: Antibiotics are effective in a select group of patients with symptoms and signs suggestive of ABRS. From the limited data available (two studies versus one) it seems that amoxicillin/penicillin (beta-lactams) especially are effective, and moxifloxacin (fluoroquinone) is not. The efficacy of beta-lactams is evident on day three where patients already experience better

symptom improvement and continue with a higher number of cures at completion of treatment. However, careful patient selection for those with ABRS is needed to avoid unnecessary use of antibiotics and side effects.[7]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Sinusitis report** and aims to provide recommendations to aid in the management of Sinusitis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Sinusitis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Sinusitis Scope

Section	Rationale/updates
NICE Guidelines for acute sinusitis (Antimicrobial prescribing) [2017]	**N/A**
American academy of Otolaryngology–Head and Neck Surgery Guidelines [2015]	This is an update of the 2007 guideline. • Acute bacterial rhinosinusitis (ABRS) should be distinguished from acute rhinosinusitis due to viral respiratory infections and noninfectious conditions. ABRS should be diagnosed when signs and symptoms of acute rhinosinusitis (ARS) (purulent nasal drainage plus nasal obstruction, facial pain-pressure, or both) persist without improvement for at least 10 days or if signs and symptoms worsen within 10 days after initial improvement. • Radiographic imaging should *not* be performed in patients with ARS unless a complication or alternative diagnosis is suspected. • Analgesics, intranasal steroids and/or nasal saline irrigation may be recommended for symptomatic relief of viral or bacterial rhinosinusitis. • Adults with uncomplicated ABRS should be either offered watchful waiting or prescribed antibiotic therapy. Patients undergoing watchful waiting should be prescribed antibiotics if their symptoms fail to improve after 7 days or worsen at any time. • If a decision is made to treat ABRS with antibiotics, amoxicillin with or without clavulanate should be prescribed as first-line therapy for 5-10 days. Amoxicillin with clavulanate should be prescribed for patients at high risk of being infected by an organism resistant to amoxicillin. • Patients with an allergy to penicillin should be prescribed doxycycline or a respiratory

	quinolone as first-line therapy. • For patients who fail to improve or worsen by 7 days following initial treatment, they should be reassessed to confirm the diagnosis and to detect complications. If initial treatment involved watchful waiting, antibiotics should be prescribed. If initial treatment included an antibiotic, a different antibiotic should be prescribed. • Chronic rhinosinusitis (CRS) and recurrent acute rhinosinusitis should be distinguished from isolated episodes of ABRS. • The diagnosis of CRS should be confirmed with documentation of sinonasal inflammation using anterior rhinoscopy, nasal endoscopy, or computed tomography. • Saline nasal irrigation, intranasal corticosteroids, or both should be prescribed for symptom relief in patients with CRS. Testing for allergy and immune function may be obtained when evaluating a patient for CRS or recurrent ARS.
American college of physicians Guidelines [2016]	**N/A**
Saudi national antimicrobial therapy Guidelines [2018]	**N/A**
International Forum of Allergy & Rhinology Guidelines [2016]	International Consensus Statement on Rhinology and Allergy: Rhinosinusitis [2021] **Management of RS** Evidence-Based Medical Management Recommendations for RS • Corticosteroids: ➔ Intranasal Corticosteroids (INCS): INCS should be used as monotherapy in mild to moderate ARS or as adjuvant to antibiotic therapy in severe cases of ARS. Policy Level: Use of INCS: Strong recommendation. ➔ Oral Corticosteroids: Systemic corticosteroids may be useful with severe facial pain or

	headaches secondary to ARS, otherwise no tangible benefit. No role as monotherapy for ARS. Policy Level: No recommendation **<u>Management of RARS (Recurrent Acute Rhinosinusitis)</u>** • Option for use of INCS spray for sinonasal symptoms during acute exacerbations of RARS. Policy Level: Option • Endoscopic Sinus Surgery: ESS (Endoscopic Sinus Surgery) or BSD (Balloon Sinus Dilation) is recommended for patients with RARS. Policy Level: Recommendation **<u>Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)</u>** Diagnosis • *Establishing the Diagnosis of CRS* An algorithm can be used to diagnose CRS. Aside from the presence of 2 cardinal symptoms for ≥12 weeks, the addition of 1 objective finding on CT or nasal endoscopy greatly increases diagnostic accuracy. Policy Level: Recommendation. Management • Saline nasal irrigation improves symptoms, QoL and nasal endoscopy for patients with CRSsNP. Duration of treatment should be greater than 8 weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated saline (40◦c) over room temperature saline. Devices with volume greater than 60 mL bring greater benefits. Policy Level: Recommendation • Topical Corticosteroids: Standard Delivery (Sprays): Standard metered dose INCS could be used in treatment of CRSsNP, particularly if primary symptoms are that of rhinitis. Policy Level: Option • Intranasal Corticosteroids (Nonstandard Delivery) for CRSsNP: Corticosteroid nasal irrigations are recommended in CRSsNP in postoperative patients and an option in nonsurgical/medical therapy patients. The use of atomizers/exhalational devices is an option. No recommendation for MAST. Policy Level: Irrigations – Recommended in postoperative patients, option for use in non-surgical/medical therapy patients. Atomizers/exhalational devices - Option. MAST – No recommendation

	• Oral Corticosteroids: The use of oral corticosteroid in CRSsNP is an option and should be individualized based on patient preference and co-morbidities. Recommendation Level: Option • Macrolide Antibiotics: Macrolides are an option for patients with CRSsNP, especially for patients at low risk of harm. Policy Level: Option • Xylitol: Xylitol is an option for treating CRS. Policy Level: Option • Colloidal Silver: Recommendation against use in CRS • Capsaicin: Use of topical capsaicin as an adjunct treatment for CRS. Policy Level: Option **<u>Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)</u>** Management • Nebulized saline (5 mL) treatment is an option for treating CRSwNP, particularly patients with thick mucus. Policy Level: Option • Intranasal Corticosteroids (Standard Delivery) for CRSwNP: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing or additional short-term corticosteroid drop if initial treatment effect is small. Policy Level: INCS: Strong Recommendation. Twice Daily Dosing: Option. High concentration/dose: No recommendation due to mixed and insufficient evidence. • Intranasal Corticosteroids (Nonstandard Delivery) for CRSwNP: Following sinus surgery, those patients with CRSwNP that have moderate-severe disease or are not controlled with simple INCS should be offered corticosteroid irrigation and/or atomized delivery. Policy Level: Corticosteroid Irrigation: Strong Recommendation. Exhalation delivery: Option. Atomization/nebulization: Recommendation. Direct injection: No recommendation due to insufficient evidence. *<u>Steroid Eluting Implants</u>* • Corticosteroid-eluting implants can be considered as an option in a previously operated ethmoid cavity with recurrent nasal polyposis. Policy Level: Option • Oral Corticosteroids: Strong recommendation for the use of oral corticosteroids in the

	short-term management of CRSwNP. Longer term use of steroids for CRSwNP is not supported by the literature and carries an increased risk of harm to the patient. Policy Level: Strong recommendation for short-term use *Biologic Therapy* • **Dupilumab**: Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options. Policy Level: Recommendation for dupilumab in patients with severe CRSwNP. *Aspirin Desensitization for AERD* • Aspirin desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence. Policy Level: Recommendation **AFRS (Allergic Fungal Rhinosinusitis) Management** • Antifungal Therapy: Can consider topical or oral antifungals in AFRS patients recalcitrant to maximal topical steroid therapy and immunotherapy. Policy Level: Option • Immunotherapy: Immunotherapy remains a reasonable treatment option. Policy Level: Option. • Anti-IgE: Consider use in difficult to treat AFRS patients with persistent thick mucoid and inflammatory discharge despite topical steroid therapy. Policy Level: Option **Acute Exacerbation of Chronic Rhinosinusitis (AECRS)** In summary, clinical studies for the management of AECRS are still lacking and further high-quality studies are needed in this area. Because of the paucity of evidence, no recommendation is currently possible. **Indications for Sinus Surgery** *Appropriate Medical Management:* For CRSsNP: Appropriate medical therapy prior to surgical intervention should include INCS, saline irrigations, and antibiotics. Oral corticosteroids are an option. For CRSwNP: Appropriate medical therapy prior to surgical intervention should include a trial of INCS, saline irrigations, and a single short course of oral corticosteroids. Oral antibiotics are an option. Policy level: Recommendation, though weak based on strength of evidence.

	Preoperative Corticosteroids: INCS are recommended prior to ESS in CRSsNP. Policy level: Recommendation for INCS. No recommendation for oral corticosteroids. **<u>Pediatric Rhinosinusitis (PCRS)</u>** *Management of ARS* • Given the likely viral etiology, antibiotics should not be given for the first 10 days of uncomplicated acute rhinosinusitis: Antibiotics should not be given for the first 10 days of uncomplicated ARS: Policy Level: Recommendation. • For patients without penicillin allergy, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as 2 nasal symptoms lasting greater than 10 days, or acute onset of severe symptoms): For patients without penicillin allergies, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as 2 nasal symptoms lasting greater than 10 days). Policy Level: Recommendation.
American College of Allergy, Asthma & Immunology updated practice parameters [2014]	**N/A**
N/A	Fokkens WJ, Lund VJ, Hopkins C, et al. **European Position Paper on Rhinosinusitis and Nasal Polyps 2020**. *Rhinology*. 2020;58(Suppl S29):1-464. Published 2020 Feb 20. doi:10.4193/Rhin20.600 • ***Treatment evidence and recommendations for adults and children with* <u>acute viral rhinosinusitis (common cold) *</u>** • **Decongestant** (oral / nasal) Ia the current evidence suggests that multiple doses of decongestants may have a small positive effect on subjective measures of nasal congestion in adults with the common cold. Decongestants do not seem to increase the risk of adverse events in adults in the short term. • Paracetamol (**Acetaminophen**) Ia Paracetamol may help relieve nasal obstruction and rhinorrhea but does not appear to improve other cold symptoms (including sore throat,

	malaise, sneezing and cough). • **NSAIDs** Ia NSAIDs do not significantly reduce the total symptom score, or duration of colds. However, for outcomes related to the analgesic effects of NSAIDs (headache, ear pain and muscle and joint pain) NSAIDs produce significant benefits, and malaise shows a borderline benefit, although throat irritation is not improved. Chills show mixed results. For respiratory symptoms, cough and nasal discharge scores are not improved, but the sneezing score is significantly improved. There is no evidence of increased frequency of adverse effects in the NSAID treatment groups. • **Antihistamine-decongestant**-analgesic combinations Ia Antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children with common cold. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children. • **Ipratropium bromide** Ia the existing evidence suggests that ipratropium bromide is likely to be effective in ameliorating rhinorrhea. Ipratropium bromide has no effect on nasal congestion and its use is associated with more side effects compared to placebo or no treatment although these appeared to be well tolerated and self-limiting. • Steam / heated humidified air 1a (-) The current evidence does not show any benefits or harms from the use of heated, humidified air delivered for the treatment of the common cold. • **Probiotics** Ia Probiotics may be more beneficial than placebo for preventing acute URTIs. However, the quality of the evidence was (very) low. • **Vitamin C** Ia Given the consistent effect of vitamin C on the duration and severity of colds in regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them. • Exercise Ia Regular, moderate-intensity exercise may influence the prevention of the common cold. • **Echinacea** 1a (-) Echinacea products have not been shown to provide benefits for treating colds, although, there could be a weak benefit from some Echinacea products:

	the results of individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance. • **Zinc** Ia Zinc administered as zinc acetate or zinc gluconate lozenges at a dose of >=75 mg/day and taken within 24 hours of onset of symptoms significantly reduces the duration of common cold. For those considering using zinc it is advised to use it at this dose throughout the cold. Regarding prophylactic zinc supplementation, currently no firm recommendation can be made because of insufficient data. • **Fusafungine** Ia Fusafungine is an effective treatment of common cold especially when administered early. However, serious allergic reactions involving bronchospasm although rare have occurred after the use of fusafungine. For that reason, the medication is no longer on the market. • ***Treatment evidence and recommendations for adults <u>with acute post-viral rhinosinusitis.</u>*** • Antibiotics 1a (-) There is no benefit from prescribing antibiotics for post viral ARS in adults. There is no effect on cure or duration of disease and there are more adverse events. Based on the moderate level of evidence and the fact that acute post-viral rhinosinusitis is a self-limiting disease, the EPOS2020 steering group advises against the use of antibiotics for adults in this situation. • Nasal corticosteroids 1a Nasal corticosteroids are effective in reducing total symptom score in adults suffering from acute post-viral rhinosinusitis. However, the effect is small. Nasal corticosteroids have not been shown to influence QOL. Acute post-viral rhinosinusitis is a self-limiting disease. Based on the moderate quality of the evidence and the small effect size the EPOS2020 steering group advises only to prescribe a nasal corticosteroid when reduction of the symptoms of the acute post-viral rhinosinusitis is considered necessary. • Systemic corticosteroids 1a Systemic corticosteroids, with or without antibiotics do not have a positive effect on recovery at 7-14 days. There is a small but significant effect of systemic corticosteroids versus placebo on facial pain at days 4-7 after start of the treatment. There are no studies comparing systemic corticosteroids to nasal

	corticosteroids. The quality of the evidence is low. Based on the evidence, the numbers needed to treat and the potential harm of systemic corticosteroids, the EPOS2020 steering group advises against the use of systemic corticosteroids in patients suffering from acute post-viral rhinosinusitis • ***Treatment evidence and recommendations for <u>children with acute post-viral rhinosinusitis.</u>*** • Antibiotics 1a (-) The use of antibiotics in children with acute post-viral rhinosinusitis is not associated with greater cure/significant improvement. Based on the moderate level of evidence and the fact that acute post-viral rhinosinusitis is a self-limiting disease, the EPOS2020 steering group advises against the use of antibiotics for children in this situation. • Nasal corticosteroids 1a Nasal corticosteroids seem to be effective in reducing total symptom score in children suffering from acute post-viral rhinosinusitis on top of (ineffective) antibiotics. Acute post viral rhinosinusitis is a self-limiting disease. Based on the very low quality of the evidence the EPOS2020 steering group cannot advise on the use of nasal corticosteroids in children with acute post-viral rhinosinusitis. • ***Treatment evidence and recommendations for <u>adults with acute bacterial rhinosinusitis (ABRS).</u>*** • Antibiotics 1a Antibiotics are effective in a select group of patients with symptoms and signs suggestive of ABRS. From the limited data available (two studies versus one) it seems that amoxicillin/penicillin (beta-lactams) especially are effective, and moxifloxacin (fluoroquinone) is not. The efficacy of beta-lactams is evident at day three where patients already experience better symptom improvement and continue with a higher number of cures at completion of treatment. However, careful patient selection for those with ABRS is needed to avoid unnecessary use of antibiotics and side effects. • ***Treatment evidence and recommendations for children with <u>acute bacterial rhinosinusitis (ABRS).</u>*** • Antibiotics 1a (-) Data on the effect of antibiotics on the cure/improvement of symptoms in ABRS in children are very limited. There are only two studies with limited numbers

	that do not show a significant difference over placebo but do show a significant higher percentage of adverse events. Larger trials are needed to explain the difference between adults where antibiotics in ABRS have been shown to be effective and this outcome. • ***Treatment evidence and recommendations for <u>adults with chronic rhinosinusitis</u>*** • Systemic corticosteroids 1a ¸ A short course of systemic corticosteroid, with or without local corticosteroid treatment results in a significant reduction in total symptom score and nasal polyp score. Although the effect on the nasal polyp score remains significant up to three months after the start of treatment, by that time there is no longer an effect on the symptom score. The EPOS2020 steering group felt that 1-2 courses of systemic corticosteroids per year can be a useful addition to nasal corticosteroid treatment in patients with partially or uncontrolled disease. A short course of systemic corticosteroid postoperatively does not seem to influence quality of life. Systemic corticosteroids can have significant side effects. • ***Pediatric chronic rhinosinusitis*** • ***Concomitant diseases in chronic rhinosinusitis***
N/A	Rank MA, Chu DK, Bognanni A, et al. **The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis**. J Allergy Clin Immunol. 2023;151(2):386-398. doi: 10.1016/j.jaci.2022.10.026 ➔ Question 1: Should INCS (topical corticosteroid), rather than no INCS, be used in CRSwNP (Chronic rhinosinusitis without nasal polyps)? Recommendation 1: In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation based on low certainty of evidence). Factors driving recommendation type: The small-to-moderate treatment effect and low certainty evidence when all 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. ➔ 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). Factors driving recommendation type: The varying values and preferences among different populations of individuals with CRSwNP drove the conditional recommendation. ➔ Question 3: Should ATAD (Aspirin therapy after desensitization), rather than no ATAD, be used in people with AERD (Aspirin (nonsteroidal anti-inflammatory)-exacerbated respiratory disease)? Recommendation 3: In people with AERD, the guideline panel suggests ATAD rather than no ATAD (conditional recommendation based on moderate certainty of evidence). Factors driving recommendation type: The benefit of ATAD is moderate and is balanced by the risk of adverse effects that can lead to discontinuation.
N/A	Kim SL, Rank MA, Peters AT. **The chronic rhinosinusitis practice parameter.** ***Ann Allergy Asthma Immunol***. 2023;131(3):307-310. doi: 10.1016/j.anai.2022.12.022 ➔ The practice parameter provides evidence-based guidelines on the use of intranasal corticosteroids (INCS) and biologics for CRSwNP, and aspirin therapy after desensitization (ATAD) for the management of aspirin-exacerbated respiratory disease (AERD). • The chronic rhinosinusitis with nasal polyps (CRSwNP) practice parameter focuses on evidence-based guidance on intranasal (topical) corticosteroids (INCS), biologics, and aspirin therapy after desensitization (ATAD). • The guideline panel suggested INCS rather than no INCS in patients with CRSwNP, and that patient-important outcomes differ by delivery method. • The guideline panel suggested biologics rather than no biologics in patients with CRSwNP, and among biologics, **dupilumab** and **omalizumab** are among the most effective. • The guideline panel suggested ATAD rather than no ATAD in patients with AERD;

	however, between a biologic and ATAD, a biologic is likely to be safer and more effective. Dupilumab, Omalizumab (both SFDA registered)
N/A	Park DY, Choi JH, Kim DK, et al. Clinical Practice Guideline: **Nasal Irrigation for Chronic Rhinosinusitis in Adults. *Clin Exp Otorhinolaryngol*. 2022**;15(1):5-23. doi:10.21053/ceo.2021.00654 • Nasal saline irrigation: Clinicians should recommend nasal saline irrigation to patients with chronic sinusitis or those who have undergone endoscopic sinus surgery. Strong recommendation • Saline tonicity: Clinicians may recommend using isotonic saline as a nasal irrigation solution for patients considering cost, convenience, and safety. However, it is unclear whether there is a clear difference in the therapeutic effect of hypertonic and isotonic saline solutions. Option • Saline temperature: Clinicians may recommend using room-temperature saline (around 20°C) as a nasal irrigation solution for patients considering effectiveness and convenience. If the patient prefers, then it is also completely acceptable to use a saline solution heated to 40°C. However, it is not recommended to immediately use a solution that has been refrigerated or to use a hot solution that exceeds 40°C for safety reasons. Option • Steroid solution: Clinicians may recommend nasal irrigation with solutions containing steroids to patients with chronic rhinosinusitis who have undergone endoscopic sinus surgery. Option • Irrigation solution preparation: Clinicians should recommend an appropriate irrigation fluid preparation method for patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. For irrigation fluid, bottled or distilled water should preferably be used. If tap water is used, boil it for at least 5 minutes and cool before use or expose it to ultraviolet light for at least 45 seconds. Recommendation • Equipment Clinicians should recommend nasal irrigation performed by high-volume with low- or high-pressure delivery rather than low-volume with low- or high-pressure

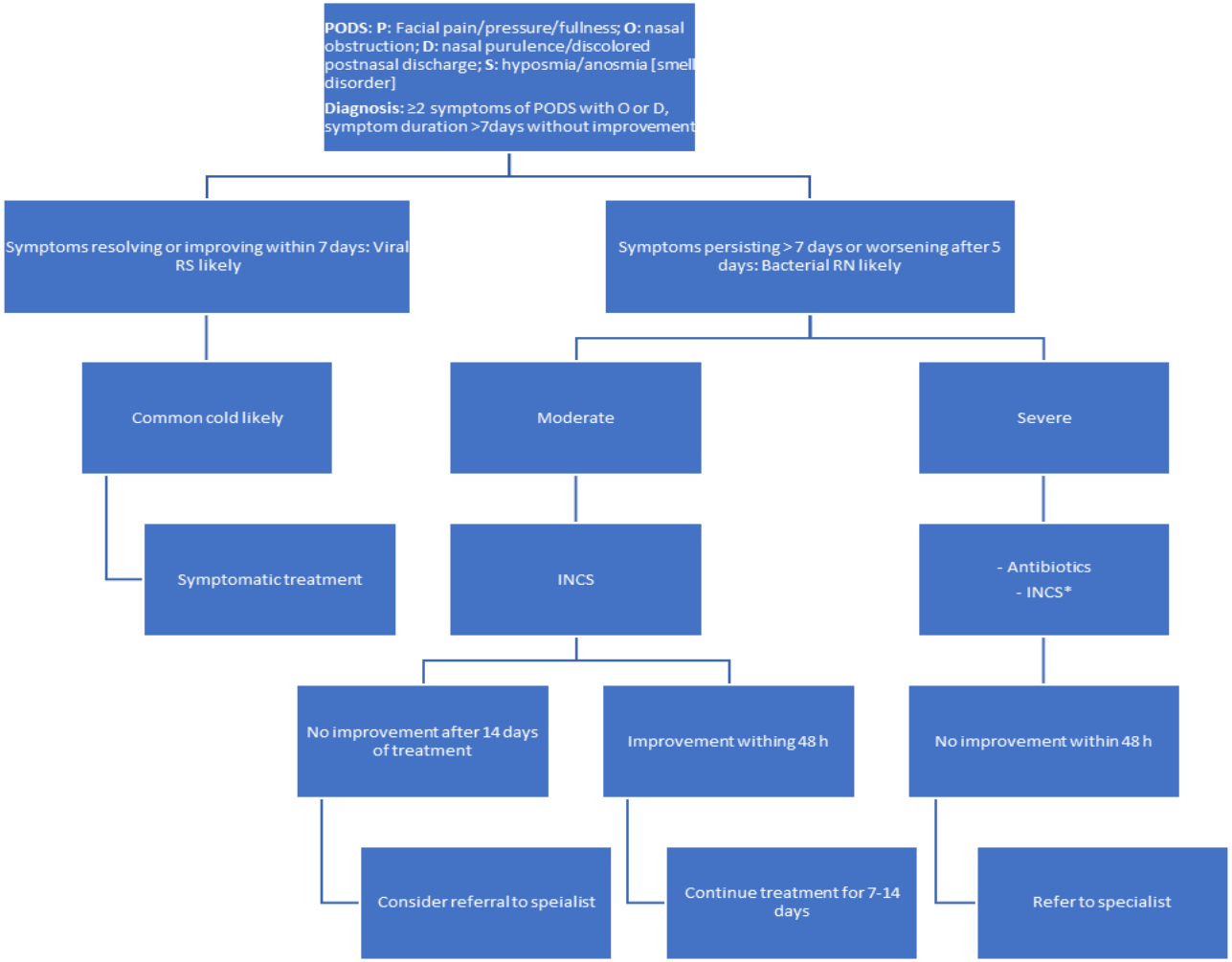
	delivery in patients with chronic rhinosinusitis. Recommendation • Disinfection: Clinicians should recommend the following techniques for appropriate irrigation equipment care to patients with chronic rhinosinusitis or those who have undergone endoscopic sinus surgery. Irrigation equipment (according to the equipment material and manufacturer's recommendations, if possible) should be boiled (for more than 2 minutes) or microwaved for 1 minute and 30 seconds regularly before and after use. Recommendation
N/A	Hopkins C, McKenzie JL, Anari S, et al. **British Rhinological Society Consensus Guidance on the use of biological therapies for chronic rhinosinusitis with nasal polyps**. *Clin Otolaryngol*. 2021;46(5):1037-1043. doi:10.1111/coa.13779 Patient with CRS with nasal polyps AND moderate symptom severity or more (SNOT22 ≥ 21 or VAS ≥ 4) AND Lund-Mackay CT Score ≥ 8 AND a score of 5 points or more out of a possible 7 Number of courses of OCS (Oral corticosteroids) in last 12 months (to max of 2 points) 1 course in last 12 months = 1 point 2 or more courses in last 12 months = 2 points Unable to take OCS due to medical contraindicators = 2 points Number of previous surgeries for CRSwNP (to max of 3 points) 1 previous sinus surgery = 1 point 2 previous sinus surgeries = 2 points 3 or more previous sinus surgeries = 3 points If unfit for surgery = 3 points Comorbid asthma = 1 point Comorbid N-ERD = 1 point in addition to 1 point for co-morbid asthma

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Sinusitis:

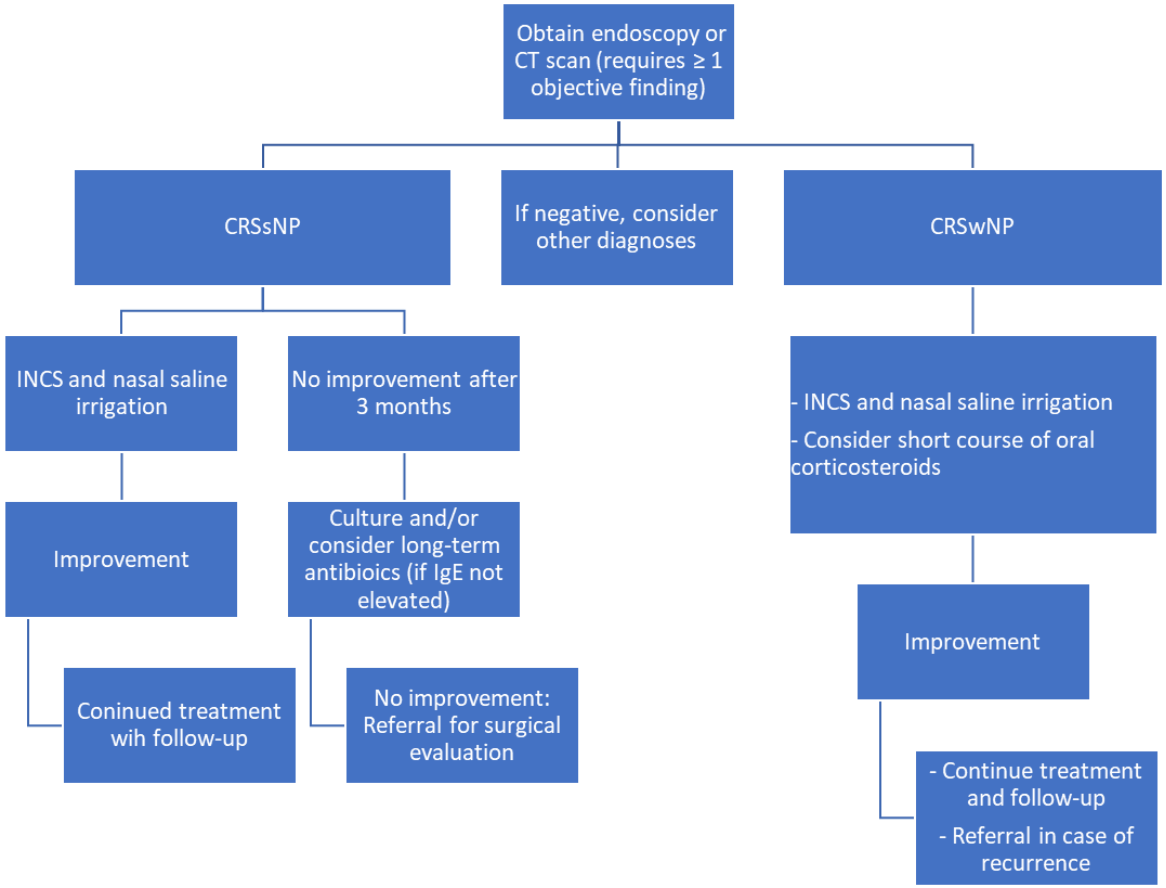
Query	Filters	Search Details	Results
((((((Sinusitis [MeSH Terms]) OR (Sinusitis [Title/Abstract])) OR (Sinusitides[Title/Abstract])) OR (Sinus Infections[Title/Abstract])) OR (Infection, Sinus[Title/Abstract])) OR (Infections, Sinus[Title/Abstract])) OR (Sinus Infection[Title/Abstract])	Guideline, in the last 5 years	("Sinusitis"[MeSH Terms] OR "Sinusitis"[Title/Abstract] OR "Sinusitides"[Title/Abstract] OR "sinus infections"[Title/Abstract] OR "infection sinus"[Title/Abstract] OR "infections sinus"[Title/Abstract] OR "sinus infection"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline [Filter]))	14

Appendix D. Treatment Algorithm



*INCS: Intranasal Corticosteroid

***Figure 2**. Treatment algorithm for the management of adults with acute rhinosinusitis*



CRSsNP: Chronic Rhinosinusitis without nasal polyps. **CRSwNP**: Chronic Rhinosinusitis with nasal polyps. **INCS**: Intranasal Corticosteroid

Figure 3. *Treatment algorithm for the management of adults with chronic rhinosinusitis*