Chapter 4

# Medical Management of the Paranasal Sinus Infections

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Additional information is available at the end of the chapter

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**Abstract**

Rhinosinusitis is a common disease among all the sinus diseases, and unsuccessful attempts to these infections may result not only in economic burdens but also in increasing the numbers of untreated patients in the community. Medical management of the rhinosinusitis includes antibiotics, antihistamines, nasal decongestants, corticosteroids, mucolytics, leukotriene antagonists, and nasal irrigations. Each treatment option must be selected for appropriate patient and prescriptions must be tailored according to the patient's need. These needs must depend on the endoscopic examination, symptoms, and sinus cultures and computed tomography. It is also a matter of debate whether these investigations lead to treatment or not, but it would be wrong to expect that a single examination method and physical examination alone should direct treatment in the first place. As a result, managing the process with the most appropriate examination methods for the patient's complaints will be the most beneficial approach.

**Keywords:** acute rhinosinusitis, chronic rhinosinusitis, pediatric, adult, nasal polyp, antibiotic

## 1. Introduction

Rhinosinusitis is the major public health problem among the upper respiratory tract infections that produce enormous consequences that source the negative effect on the quality of life of the patient and cause significant morbidity and mortality. Rhinosinusitis also has a significant effect on the health economics. In the United States, the predicted yearly amount of the burden has been estimated at $3.5–5.8 billion, especially $1.8 billion for first 12 years of age [1]. It seems that rhinosinusitis affect the quality of life of the children and cause economic loss. It is imperative to obtain up-to-date and accurate information for each physician who is involved in the treatment of this disease group and related ones. In this chapter, updated

information has been given about the medical treatments on pediatric acute rhinosinusitis, pediatric chronic sinusitis, adult acute rhinosinusitis, adult chronic rhinosinusitis without nasal polyp (CRSsNP), and adult chronic rhinosinusitis with nasal polyp (CRSwNP). This information has been compiled from very important guidelines and articles by authors. In this way, the reader will be able to acquire much more detailed and accurate information as well as the source of the information to be obtained.

## 2. Medical management of pediatric acute rhinosinusitis

### 2.1. Oral antibiotics

Oral antibiotic treatment is not necessitating the majority of the acute rhinosinusitis (ARS) patients. Viral infections that resolve without therapy are the main cause of rhinosinusitis [2]. A minor proportion of these patients develop a subsequent bacterial inflammation that will heal with antimicrobial treatment. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, Group A beta-hemolytic *streptococci,* and *Staphylococcus aureus* are the most common cause of the development of rhinosinusitis. Therefore, the patient who has taken oral antibiotic therapy is the most important concern in clinical practice. However, acute rhinosinusitis with viral etiology may be resolved without any treatment but bacterial rhinosinusitis is treated by antibiotics. The diagnosis of bacterial ARS may be considered when symptoms prolonged over 10 days or there is deterioration after drug-free follow-up period [3]. The guideline from the American Academy of Pediatrics [4] suggested that physicians must use antibiotic treatment for ARS in children with intense beginning or deteriorating progression. As well, reporters also advised that physicians should either use antibiotic therapy or offer further outpatient observation for 3 days to children with persistent disorder. This report also confirmed that if there is no improving in symptoms or if there is a failure to recover, clinicians should modify antibiotics or initiate antibiotics in child treated with observation [4]. The recommendation of using antibiotics for severe or worsening acute bacterial sinusitis in consequence of the benefits showed a theoretically higher risk of suppurative complications than for children who existed lasting symptoms.

It is recommended that when the clinical diagnosis of acute bacterial rhinosinusitis (ABRS) is established, empirical antimicrobial therapy should be initiated directly [5]. Amoxicillin-clavulanate (45 mg/kg/day, divided into two doses) instead of amoxicillin alone is recommended as the initial therapy of ABRS in children. The cephalosporins such as cefuroxime, cefdinir or cefpodoxime, clindamycin (or linezolid) + cefixime, and levofloxacin may be preferred in the condition of a penicilin allergy. Cephalosporins are usually used as the suitable treatment for ARS. Cephalexin and cefadroxil, which are the first-generation agents, are not the first choice for *H. influenzae* infection. Beta-lactamase-producing *M. catarrhalis* and some *H. influenzae* strains has reduce the response to cefaclor (50 mg/kg/day in two doses), and early second-generation cephalosporins. On the other hand, beta-lactamase-producing bacteria have a good response to second-generation cephalosporins (cefuroxime axetil, 30 mg/kg/day and cefprozil, in two doses as oral suspension). Third-generation cephalosporins such

as cefixime, ceftibuten, cefpodoxime axetil (10 mg/kg once daily), and cefdinir (14 mg/kg/day in one or two doses) seem to be an alternative option for the therapy. Macrolides (clarithromycin and azithromycin) are not recommended for empirical treatment due to elevated resistance rates of *S. pneumoniae*. Because of high resistance rates between *S. pneumoniae* and *Haemophilus influenzae*, trimethoprim-sulfamethoxazole is not recommended for empirical treatment. Ampicillin-sulbactam (100 mg/kg/day for three times a day) or ceftriaxone (100 mg/kg/day at single or double dose) given intravenously or intramusculary can be used in patients who do not endure oral antibiotics due to vomiting or in patients who do not recover after 24–48 hours of treatment with a second antibiotic therapy. If there is a suspicion of an aerobic pathogen as a cause of ARS, clindamycin or metronidazole may be added to a wide spectrum antibiotics. In patients with acute bacterial RS, the appropriate treatment duration is not definitively defined, but 10–14 days of treatment appear to be adequate for mild acute forms, but 14–21 days of treatment appear to be appropriate for severe acute forms and subacute forms [5].

### 2.2. Intranasal saline irrigation

Nasal saline irrigation has been shown to be effective and well tolerated in children with rhinosinusitis [6]. Management of sinus disease often involves the use of saline irrigations. Saline irrigation helps patients with rhinosinusitis by improving mucociliary clearance, slenderizing mucus, and providing anti-inflammatory effects [7]. Decreasing in symptoms after nasal irrigations is associated with an increase in quality of life in patients with acute rhinosinusitis [3, 8, 9].

### 2.3. Intranasal corticosteroids

It has been also shown that the use of intranasal corticosteroids significantly improved the symptoms of ARS [3]. Intranasal corticosteroids are recommended for both moderate (monotherapy) and severe (oral antibiotics) types of acute rhinosinusitis [10]. A double-blind, placebo-controlled trial revealed the efficacy of topical corticosteroid therapy in comparison with both monotherapy and antibiotics [11]. In this study, mometasone furoate (MF) was compared with amoxicillin and placebo in patients with ARS. MF 200 μg twice a day was significantly better than placebo and amoxicillin for correction of symptom score. MF was used once a day and was superior to placebo but not to amoxicillin. This study is the first study to show that topical corticosteroids are effective when given twice daily in the treatment of ARS and are more effective than amoxicillin. The results of this study were also supported by two other studies with a similar design. However, in another study, the use of antibiotics and topical steroids alone and in combination has not been effective in changing the severity of symptoms or duration of bacterial ARS. However, in this study, the patients with 4 days of symptoms and only those with colds and not ARS have been included. It is supported by the use of intranasal corticosteroids alone or as adjuvant therapy to antibiotics. High doses of intranasal corticosteroids (mometasone furoate 400 versus 200 μg) have a stronger effect on the reduction or complete improvement of symptoms. There was no significant adverse effect for both treatment groups, and there was no significant difference in the reduction in

symptoms and recurrence rates with higher doses of intranasal corticosteroids. Further randomized clinical trials are needed to examine the effectiveness and proper use of antibiotics and intranasal corticosteroids as a single or combined therapy for the treatment of different severe ARS. There are some studies comparing the effectiveness of mometasone furoate nasal spray and amoxicillin and placebo in patients with acute, uncomplicated RS. It is concluded that the use of mometasone furoate twice daily as 200 μg in acute, uncomplicated RS patients significantly reduced symptoms when compared with amoxicillin and placebo without predisposing factors or bacterial infection [12]. Rahmati et al. [13] revealed that the use of fluticasone in children has been associated with reducing the severity of acute sinusitis symptoms. Foden et al. [7] stated that intranasal corticosteroids (INCS) are the basis for the treatment of rhinosinusitis. As a monotherapy in ARS, INCS had a significant improvement in symptoms compared to placebo and amoxicillin [12]. On regarding the use of INCS, either as monotherapy or adjuvant to antibiotics, these studies have also been designed based on the approval of diagnosis. Intranasal corticosteroids (INCSs) are recommended in patients with a history of allergic rhinitis, especially as an adjunct to antibiotics for the empirical treatment of ABRS [5].

### 2.4. Other treatment modalities

It was accepted as a symptomatic treatment of viral upper respiratory tract infections with analgesic, antipyretic, and decongestant drugs (topical or systemic) [6]. Decongestants should be used with caution in pediatric patients because there is a small number of studies on the efficacy and side effects of decongestants. Concurrent use of decongestant and antihistamine in the treatment of pediatric upper respiratory tract infection and inflammation is still debated. In patients with ABRS, topical or oral decongestants and/or antihistamines are not recommended as adjuvant therapy (strong, low to moderate). Oral corticosteroids may be added to the treatment of cases with nasal polyposis or marked mucosal edema when the initial treatment is not received [14]. Antihistamines are useful in the case of accompanying acute bacterial RS and allergic RS because they reduce the inflammatory component and respond positively to antibiotics. Except the current allergic rhinitis, there is no indication for the use of antihistamines (both intranasal and oral) in the treatment of postviral ARS [10].

### 2.5. Nonresponsive patients

The patients who have worsened clinically during the first 72 hours or who have not recovered after 3–5 days of empirical antimicrobial therapy with a first-step agent should be evaluated for resistance pathogens, nontoxic etiology, structural abnormality, or other reasons for treatment failure (strong, low). In patients with suspected sinus infection who cannot respond to empirical antimicrobial therapy, cultures are recommended to be obtained with direct sinus aspiration rather than nasopharyngeal swab (strong, moderate). Endoscopic-guided cultures of medium meatus may be considered as an alternative in adults, but their reliability was not determined in children (weak, moderate). Nasopharynx cultures are not considered reliable and are not recommended for microbiological diagnosis of ABRS [5].

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## 3. Medical management of pediatric chronic rhinosinusitis

### 3.1. Intranasal saline irrigation

Nasal saline irrigation should be considered as the primary therapeutic tool in CRS, even in the child age group, which is a long-term CRS [15–17]. Nasal saline lavage can significantly reduce chronic sinusitis symptoms, improve disease-specific quality of life, and be well tolerated in children with chronic rhinosinusitis symptoms [6, 18]. Nasal saline solutions make it easier to mechanically remove the mucus and increase the ciliary rhythm [19]. Nasal saline sprays or irrigations when tolerated are also used in the treatment of CRS, and primarily, sinonasal secretion, pathogens and debris removal are thought to help. Although Cochrane collection does not support any advice on nasal saline irritation, some studies have shown some degree of efficacy in CRS [16].

### 3.2. Intranasal corticosteroids

Topical steroids, although the absolute resolution of the CRS does not improve, may accelerate the solution of CRS symptoms when evaluated in the short term. In the management of CRS, it may be affected by suspected or proven allergic disease, including steroids. In particular, nasal steroids should be maintained when an allergic patient is treated for CRS. Topical nasal steroids suppress mucosal inflammation [9]. Examples include fluticasone propionate, commonly found in generic form, and mometasone furoate, which is indicated for use in nasal congestion due to allergic rhinitis in children aged 2 years and older. Topical nasal steroids are usually preferred for children with CRS due to low systemic bioavailability. Therefore, systemic side effects are rare in children with CRS and the most common complication is epistaxis. Although long-term prophylactic use often seems to be safe, it helps to suppress chronic symptoms and recurrent diseases, and typically conflicts with long-term antibiotic medicines used in CRS every 3–6 weeks [16].

### 3.3. Antibiotic treatment in the management of pediatric chronic rhinosinusitis

#### *3.3.1. Oral antibiotics*

Long-term and broad-spectrum antibiotics have been the basis for treating pediatric chronic rhinosinusitis. Amoxicillin/clavulanate is a good choice for first-line treatment, but antibiotics to be selected must also be effective against possible pathogens in CRS, including *S aureus*, Pseudomonas and anaerobes. Encompassing for MRSA may be indicated. Long-period treatment with macrolides for up to 12 weeks may also benefit patients with CRS. A culture should be obtained, preferably directly from the sinus cavity or endoscopic, in patients who do not recover or develop worsening despite treatment. For the last 20 years, antimicrobial resistance has been increasing. These contain the creation of beta lactamases and cephalosporins. Clindamycin can be administered in the event of penicillin allergy or who suspect MRSA. Other oral agents covering MRSA include trimethoprim-sulfamethoxazole and linezolid. The dose of amoxicillin-clavulanate recommended for children is 45 mg/kg. Another

recommended antibiotic management procedure is high-dose amoxicillin or amoxicillin/clavulanate (90 mg/kg/day orally twice daily) for children from environmental areas with high endemic degrees (>10%) of aggressive penicillin-nonsusceptible (PNS) *S. pneumoniae*. In addition, high-dose amoxicillin or amoxicillin/clavulanate therapy is recommended for the children with severe infection, attendance at nursery, age<2, latest hospitalization, antibiotic usage within the past month, and immunocompromisation [6, 16, 20]. Metronidazole can be administered in addition to one of the following antibiotics: cefazolin, cefuroxime, cefixime proksetil, clarithromycin, azithromycin, or trimethoprim-sulfamethoxazole and is administered as three times a day for 30–50 mg/kg/day and maximum daily dose for 2.250 mg/day. Antimicrobial therapy is given for a three-week period and can be extended up to 10 weeks in patients with antibiotic resistance [19].

*3.3.2. Parenteral antibiotics*

Parenteral treatment is applied to children who are extremely ill, who undergo surgery or who have a problem of adaptation to the oral regimen. Among the parenteral antimicrobials such as ampicillin-sulbactam, piperacillin-tazobactam, clindamycin, moxifloxacin, carbapenems (imipenem, meropenem, doripenem), and second-generation cephalosporins, cefoxitin effective against both anaerobes and aerobes are included. Vancomycin, linezolid, and daptomycin and ceftaroline are among the parenteral antimicrobials effective against MRSA. Metronidazole may be given as parenteral against anaerobes in combination with an agent with aerobic activity [9, 20].

*3.3.3. Intranasal antibiotics*

Although topical antibiotic treatment is not recommended in the best part of CRS cases, further studies should be required according to the initial findings. Demands about the combination potential with dose, treatment time, optimal treatment method, and other therapies carry on to be responded [9].

**3.4. Systemic corticosteroids**

Oral methylprednisolone has a good tolerance and offers additional benefit to treatment with antibiotics for children with CRS [21]. Combination treatment with systemic corticosteroids and antibiotics was established to be favorable in children (age between 6 and 17 years) with CRS whose management with at least three 10–14–day sequences of wide-spectrum antibiotics was unsuccessful. Minimal side effects may be seen. It was observed that children treated with corticosteroids plus antibiotics had meaningfully better declines in entire symptom and sinus CT scores compared with those given placebo plus antibiotics. Complete clinical healing observed more frequently and reverts within 6 months less commonly in the active management group. Moreover, Ozturk et al. [21] conducted a randomized trial comparing amoxicillin-clavulanate with and without methylprednisolone, and examined the advantage of addition of systemic corticosteroids to oral antibiotics for the management of CRS. Both management arms revealed progress compared with baseline with the steroid management being meaningfully more effective regarding dropping CT

scores and total rhinosinusitis symptoms, such as nasal obstruction, cough, and postnasal drainage [22].

### 3.5. Adjuvant medical treatments

Adjuvant medical treatment involving antihistamines and decongestants for pediatric CRS has been used widely with unconfirmed benefits. Oral antihistamines and decongestants may offer symptomatic advance; but the general period of the disease may not be affected. Moreover, the effects of antihistamines and decongestants on secretions and mucosa may undesirably affect the innate physiologic mechanisms of the sinuses and nose to cope with infection and inflammation [9, 16, 19].

### 3.6. Treatment for gastroesophageal reflux

It is not proved to use proton pump inhibitors (PPI) for pediatric CRS. The International Consensus Statement on Allergy and Rhinology: rhinosinusitis [23] summaries the facts about CRS and laryngopharyngeal reflux. It has set grade B evidence to prove the relationship between these situations but expresses that treatment guidelines or mechanistic trials are requiring. This statement further endorses to establish accurately diagnosing laryngopharyngeal reflux before starting PPI management in patients with difficult to treat CRS [24].

## 4. Medical management of adult acute rhinosinusitis

### 4.1. Nasal saline spray/saline irrigation

In the treatment of adult ABRS, there has been a recommendation of topical nasal saline irrigation with either isotonic or hypertonic form as a combined treatment. Saline sprays have an effect on reducing rhinitis symptoms. Also, it revealed a better sinus-related quality of life, decreased symptoms, and drug use with routine hypertonic nasal saline irrigation. No serious side effect has been determined with saline irrigation. When compared to isotonic saline, hypertonic saline treatment may have a better anti-inflammatory result and ability to subtilize mucous and rapidly recover mucociliary clearance [5, 25].

### 4.2. Intranasal corticosteroids

In the routine treatment of acute bacterial rhinosinusitis, intranasal corticosteroids (INCSs) are recommended as a supplement to antibiotics, especially in patients with allergic rhinitis [5, 12, 26]. Intranasal corticosteroids improved the symptoms and had only minor side events, consisting of headache, nasal itching, and epistaxis [25].

### 4.3. Antibiotic treatment

In acute bacterial rhinosinusitis, the most common determined pathogens are *S. pneumoniae or H. influenzae*, so the use of amoxicillin (with or without clavulanate) is commonly recommended

for empirical treatment in adult patients [25, 27]. On the other hand, Chow et al. [5] recommends amoxicillin-clavulanate rather than amoxicillin as empirical antimicrobial therapy for ABRS in adults. Also, it is recommended to use penicillin or amoxicillin for 7–14 days [10]. Macrolides (azithromycin and clarithromycin) are not recommended for initial therapy because of high rates of resistance to *S. pneumoniae*. By the way, trimethoprim-sulfamethoxazole is also not recommended for initial therapy due to high rates of resistance to both *S. pneumoniae* and *Haemophilus influenzae*. As an alternative treatment to amoxicillin-clavulanate for empirical therapy of adult ABRS, doxycycline may be chosen for being highly effective against airway pathogens and having superb pharmacokinetic/pharmacodynamics features [5].

Because of the inconstant proportions of resistance among *S. pneumoniae*, there is no recommendation for second- and third-generation oral cephalosporin antibiotics in the initial monotherapy of ABRS. Combined treatment with a third-generation oral cephalosporin (cefpodoxime or cefixime) plus clindamycin may be used as a second-line treatment for children from geographic regions with high endemic rates of penicillin nonsusceptible *Streptococcus pneumoniae* or for children with non-type I penicillin allergy. İt is strongly recommended that the use of doxycycline, levofloxacin, or moxifloxacin may be an alternative treatment for initial antimicrobial therapy in adults who are sensitive to penicillin. According to the up-to-date data, it is not a recommended routine antimicrobial coverage for *S. aureus* or MRSA for the initial treatment of ABRS, even though *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]) is a possible agent in ABRS, and 5–7 days' therapy is recommended for uncomplicated ABRS in adults [5].

*H. influenza*e can be highly resistant to amoxicillin and ampicillin [28]. Fluoroquinolones remain highly effective against both *H. influenzae* and *S. pneumoniae* [29]. Though the role of the fluoroquinolones is growing, these drugs are commonly recommended as second-line treatment, or as first-line treatment in patients with moderate illness who have had recent antimicrobial treatment, or for clinically moderate to severe disease patients [30, 31]. In these cases, another treatment option may be using high-dose amoxicillin/clavulanate (4 g/250 mg per day). High-dose amoxicillin with clavulanate treatment (2 g orally twice daily or 90 mg/kg/d orally twice daily) is recommended for adult patients with ABRS who have high risk of being infected with an amoxicillin-resistant organism. High-dose amoxicillin/clavulanate (4 g/250 mg per day) is recommended for severe infection, findings such as evidence of temperature of 39°C [102°F] or higher and trend of suppurative complications, age over 65 years, necessity of hospitalization, antibiotic usage within the last month, immunocompromisation and living in geographic regions with high endemic rates (>10%) of invasive PNS S *pneumoniae*. Alternative treatment choice of acute rhinosinusitis comprises of cephalosporins. Third-generation cephalosporins, such as cefdinir or ceftriaxone, are enough effective against *H. influenzae* but have much lower effectiveness against *S. pneumoniae* [27].

#### *4.3.1. Penicillin-allergic patients*

Though resistance rates of macrolide antibiotics to *H. influenzae* and *S. pneumoniae* are rising throughout the world, as first-line agents in patients with β-lactam allergies, they are still preferred [31]. For these patients, either a fluoroquinolone (levofloxacin or moxifloxacin) or doxycycline is recommended as another agent for initial antimicrobial treatment. For patients who

do not have penicillin allergy, fluoroquinolones are not considered as the first-line treatment of ABRS, because results are similar to amoxicillin-clavulanate, and side effects are seen higher [27].

### 4.4. Additional treatments

Clinicians may recommend analgesics, nasal saline, and/or topical intranasal steroids, for symptomatic relief of ABRS. Nonsteroidal anti-inflammatory agents or acetaminophen are generally adequate for facial pain related to ABRS [25].

#### *4.4.1. Decongestants*

##### *4.4.1.1. Topical decongestants*

There are no recommendation about topical and oral decongestants as combined therapy. Decongestants may offer short-term relief for nasal congestion. Xylometazoline or oxymetazoline is the frequently existing topical decongestants. They can be found in the form of drops or spray and act by contracting the sinusoids in the nasal tissues. After applying these agents intranasally, within 10 minutes, local vasoconstriction occurs. Their effects last up to 12 hours. Decreased nasal mucosal blood flow and mucosal clearance may cause this long effect: the topical nasal decongestants. Topical nasal decongestants have important side effects such as nasal mucosal irritation, dryness, or ulceration. Long-term use (>10 days) of topical nasal decongestants may cause tachyphylaxis and rhinitis medicamentosa (rebound swelling of the nasal mucosa). Therefore, the use of topical nasal decongestants must be limited to 10 days [5].

##### *4.4.1.2. Oral decongestants*

Phenylephrine, pseudoephedrine, and ephedrine are frequently used as oral decongestants. As they offer rapid relief on a short term, they are preferred commonly. When compared to topical nasal decongestants, oral decongestants have a lower effect on the nasal obstruction. Because they have no effect of rebound phenomenon, they may be preferred for a long term. After oral intake, nasal decongestion starts within 30 minutes and continues for up to 6 hours. Phenylephrine is the least effective agent among the oral decongestants. There are some side effects related to the oral decongestants such as nervousness, drowsiness, agitation, and arrhythmias. There are some risks that should be avoided to use oral decongestants in combinations with alcohol or some medications such as sedatives and monoamine oxidase inhibitors. For patients with stable hypertension, commonly, there is no noteworthy rise in blood pressure. However, careful use is recommended in patients with prostatic hypertrophy, glaucoma, or ischemic heart disease [27].

#### *4.4.2. Topical anticholinergics*

Topical intranasal anticholinergics, such as ipratropium bromide, are mainly preferred to stop symptom of rhinorrhea. On nasal congestion, sneezing and itching has no significant effect. Nasal irritation, burning, and dryness are the most common adverse effects followed by a headache, dry mouth and stuffy nose, etc. On mucociliary clearance, nasal mucosal alteration, and olfaction, they have no effect with long-term usage [25].

#### *4.4.3. Antihistamines*

For management of acute rhinosinusitis, no clinical trials recommend the use of antihistamines. First-generation antihistamines have the anticholinergic effects, and thus, mucociliary clearance may be impaired. On the other hand, second-generation antihistamines have no anticholinergic effect and are not recommended for acute rhinosinusitis [25].

#### *4.4.4. Mucolytics*

As a mucolytic agent, guaiphenesin is a frequently used for mucolysis. It is commonly preferred together with a decongestant drug. While it is used to thin the nasal secretions and increase drainage, trials evaluate the effects of placebo and guaiphenesin on ciliary beat frequency and nasal mucociliary clearance, and could not reveal any assessable impact [25].

#### *4.4.5. Oral corticosteroids*

When oral corticosteroid steroids are used as monotherapy for ABRS, there is no recommendation to use of systemic steroids for ABRS and they have no advantage over placebo. Among their adverse events, in mild condition, gastrointestinal complaints, nausea, and vomiting may also be seen. But the effects of these agents must take into account on the systems of glucose metabolism, bone turnover, and cardiovascular circulation [25].

## 5. Medical management of adult chronic rhinosinusitis without nasal polyp (CRSsNP)

### 5.1. Saline treatment

Nasal saline irrigations have beneficial effects and are accepted treatment modality as strong recommendation for chronic rhinosinusitis. Among the advantageous effects of saline are healing of symptoms and improving quality of life, increase in mucous clearance, improved ciliary activity, interruption and elimination of inflammatory mediators, biofilms and antigens, and protection of the sinonasal mucosa [25]. Nasal saline treatment has beneficial safety profile, no risk of systemic absorption, and well patient tolerance make it a potent long-term topical nasal therapy approach. Irrigation solutions may be either isotonic or hypertonic saline. High-volume (>200 mL) nasal saline irrigations in addition to other medical treatments is strongly recommended for CRS. Hypertonic nasal saline irrigations notably enhanced CRS-specific quality of life, symptom scores, and diminished drug usage. For establishing the hygiene, microwave decontamination of the irrigation bottles may be considered as a useful disinfecting method. It has been established that saline irrigation is superior to saline spray in throwing out secretions and enhancing the quality of life [23, 25].

### 5.2. Intranasal corticosteroids

It has been shown that the patients with CRSsNP benefited significantly from topical nasal steroids. The direct transmission of INCS to the sinuses has a greater impact. Patients with

previous sinus surgery have a favorable impact of INCS in comparison with nonsurgical patients. INCS have only slight side effects. Modern INCS have no additional clinical effectiveness than the first-generation INCS [23, 32].

#### *5.2.1. Standard delivery (sprays)*

The standard measured dose of INCS should be used in the treatment of CRSsNP. There is a significant improvement in the endoscopic and symptom scores. Dominance of benefit outweighs harm. Aggregated degree of evidence is A. Epistaxis and headache may be seen as side effects [23].

#### *5.2.2. Nonstandard delivery (sprays)*

Penetration of topical nasal sprays behind the nasal cavities into the paranasal sinuses, especially in preoperative patients, is expected to be limited. This situation caused a need to use of new delivery devices to offer improving corticosteroid deposition in the sinus tissues and for possible clinic healing. There are four prominent nonstandard delivery methods: (i) intranasal irrigation, (ii) maxillary antrostomy sinusotomy tubes (MAST), (iii) mucosal atomization devices (MAD), (iv) YAMIK sinus catheter. As a consequence, intranasal corticosteroid irrigations are the option in CRSsNP. They may be mostly beneficial for postoperative patients. The utilization of MAST or MAD is an option. Use of the YAMIK device is not recommended based on up-to-date data [23].

### 5.3. Oral corticosteroids

There is no clear evidence on the benefits of oral corticosteroids in CRSsNP. Oral steroid usage in CRSsNP is optional, due to inadequate strong evidence. Oral steroid use in perioperative period with CRSsNP is not recommended. The risks of oral steroids are uncommon, but significant side effects should be taken into consideration [10, 23, 33].

### 5.4. Antibiotics

#### *5.4.1. Oral antibiotics*

Sabino et al. [34] stated that 14 days of amoxicillin-clavulanate usage did not change any clinical course of acute exacerbations of chronic rhinosinusitis (AECRS) compared to placebo. Interestingly, combination of an oral antibiotic with a topical intranasal steroid spray may not offer further benefits for managing AECRS. When intranasal corticosteroids and saline irrigations have failed to reduce symptoms, long-term antibiotic treatment should be considered. Macrolide antibiotics have been used in the majority of trials. These antibiotics have revealed a response proportion of 60–80%. Roxithromycin has acceptable effects in patients without polyp. In a placebo-controlled azithromycin study, [35] suggests that the population with high serum IgE are less likely to respond to macrolide treatment. Long-term treatment with doxycycline or trimethoprim-sulfamethoxazole could reveal hopeful options. Level of evidence for macrolides in patients with CRSsNP is Ib, and strength of recommendation C, but in CRSsNP patients with normal IgE, the recommendation level is A [10].

*5.4.2. Oral out of macrolide antibiotics for <3 weeks*

When considering the use of antibiotic treatment less than 3 weeks in the management of CRS, current data are related to the treatment of AECRS. In addition, there is a shortage of suitable prospective trial at present. Because there is no sufficient clinical study and data, the ability to make recommendations regarding the use of nonmacrolide antibiotic for less than 3 weeks in CRSsNP is not applicable [10].

*5.4.3. Oral out of macrolide antibiotics for >3 weeks*

Although there are significant data on the role of long-term treatment with macrolide antibiotics for CRSsNP, there are little data in the literature concerning similar management with nonmacrolide agents. Dubin et al. [36] conducted an observational study with long-term oral antibiotics in patients with CRSsNP. Thirty five patients with CT scan and culture-approved CRSsNP were prescribed antibiotics for 6 weeks. At the end of the study, there was no considerable improvement between third and sixth weeks and only 38% of the patients reported improvement in CT scan scores. For the treatment of CRSsNP, the recommendation of nonmacrolide oral antibiotics for longer than 3 weeks has inadequate evidence. So, there is no applicable degree of evidence for the use of oral nonmacrolide antibiotics in CRSsNP [23].

*5.4.4. Macrolide antibiotics*

Macrolide antibiotics have both anti-inflammatory and antimicrobial functions, and for this reason, they may be considered to be effective in the treatment of CRS. Previous studies on lower respiratory diseases have led to be used macrolide antibiotics in the treatment of CRS. In those studies, erythromycin had been used in panbronchiolitis to improve clinical symptoms. Aggregated grade of evidence of these therapeutic agents is B. They offer, especially for patients without elevated IgE, a decline in endoscopy scores and some symptoms in patients with CRSsNP. Their effects are comparable to INCS. The effect of the agents may not sustain for long term after termination of treatment. They have important risks of drug interactions, in frequent mild undesirable events, and severe cardiovascular complications. Their benefits seem to outweigh harms. The convenient drug, dosage, and length of therapy are not recognized. Macrolides have an optional effect for patients with CRSsNP and were judged for the evidence of moderate quality [37].

*5.4.5. Intravenous antibiotics*

Intravenous antibiotics have a weak evidence in the treatment of CRSsNP. Their aggregated grade of evidence is C. There has been possible healing with patient-reported symptoms in case-controlled and cohort trials. Among their side effects, bleeding, deep vein thrombosis, drug adverse events, elevated liver enzymes, neutropenia, rash, thrombophlebitis, and sepsis may be determined. Their cost is high. The harm during the use of these agents outweighs the benefits. There is no recommendation for the use of intravenous antibiotics and should not be prescribed routinely in CRSsNP [23].

*5.4.6. Topical antibiotics*

The aim of topical antibiotic treatment for CRS is to transport high amounts of antibiotics into the sinonasal tissues, hence enhancing efficiency, diminishing systemic absorption and related side effects. It has been demonstrated that endoscopic sinus surgery increases the penetration of topical antibiotic agents from 2 to more than 95%. There is an aggregated grade of evidence of B for this management strategy, but randomized controlled trials have been unsuccessful to demonstrate any benefit from the application of topical antibiotic agents. Among their side effects, epistaxis, irritation, and nasal congestion may be seen. There is no recommendation regarding the topical antibiotic treatment in the management of CRSsNP at present [10].

### 5.5. Antifungal treatment in the management of adult chronic rhinosinusitis without nasal polyp (CRSsNP)

*5.5.1. Topical antifungals*

Physicians should avoid prescribing any topical antifungal therapy for routine patients with CRSsNP due to the systemic review of randomized controlled trials. Also, clinicians must avoid cost of ineffective therapy, unnecessary side effects, and shift of sinonasal flora [10].

*5.5.2. Oral antifungals*

For a significant subgroup of patients, fungi are considered as a causative agent of CRS with eosinophilic inflammation. Hence, it has been thought that antifungals have a possible effect in this subgroup of CRS patients. So, in the standard management of CRSsNP, there has been no confirmation about the use of oral antifungal treatment and aggregated grade of evidence is not applicable [10].

### 5.6. Combination treatment with nasal irrigation treatment in the management of adult chronic rhinosinusitis without nasal polyp (CRSsNP)

The antimicrobial effects of the sodium hypochlorite (NaOCl), particularly against *S. aureus* and *P. aeruginosa*, have been well established. Topical nasal irrigation with 0.05% NaOCl in saline solution has been found to be more effective than saline alone after 3 months usage [10, 38]. For nasal irrigation, xylitol in water is a well-tolerated substance. Xylitol irrigations lead to a further healing in chronic rhinosinusitis symptoms compared to saline irrigation [10]. It is considered that biofilms have the pathophysiological role in CRS. Surfactants have reductive effects on water surface tension and may facilitate dissolving of the biofilms. The use of sodium hypochlorite or xylitol nasal irrigations is supported by up-to-date with grade of recommendations B, but baby shampoo irrigations are not supported [10].

### 5.7. Proton pump inhibitors

There is no satisfactory evidence of the use for proton pump inhibitor therapy for CRSsNP in adults. Hence, there is also no support for the use of proton pump inhibitors, H2-receptor antagonists, antacids, or prokinetic therapy for chronic rhinosinusitis [39].

### 5.8. Topical alternative therapies

#### *5.8.1. Surfactants*

The benefits of surfactants are clearance of thick secretions and interruption of biofilm formation. Surfactants have the effects of clearance of secretions and blockage of biofilm development. Their side effects comprise ciliary dysfunction and nasal irritation. Although they have balanced effects regarding benefit and harm and limited clinical information, it is not possible to recommend for the use of surfactants in CRSsNP [23].

#### *5.8.2. Manuka honey*

Manuka honey and chief component methylglyoxal have in vitro effects against both the biofilm and planktonic formations of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. But, regarding the routine use of Manuka honey in CRSsNP, no clinical study exists. Possible respiratory epithelial damage, nasal irritation, and burning may also be seen. As of the lack of evidence, it is not possible to recommend to use Manuka honey in CRSsNP [23].

#### *5.8.3. Xylitol*

Xylitol is composed of five-carbon sugar and has the property of improving the innate immune system. The main effect of xylitol is to increase the activity of natural antimicrobial factors in respiratory secretions [23].

## 6. Medical management of adult chronic rhinosinusitis with nasal polyp (CRSwNP)

### 6.1. Saline (spray and irrigation) treatment

In the management of CRSwNP, saline is strongly recommended as grade A evidence. Both isotonic and hypertonic saline irrigations seem to offer similar subjective results and are well tolerated. There is a dominance of benefit rather than harm. It is important to use nasal saline irrigation in addition to other topical treatment approaches. There is a superiority of higher volume (>200 mL) irrigations over low-volume topical nasal sprays [10, 23, 40, 41]. Regarding the patients with difficult to treat sphenoid sinus disease, it has been suggested that the irrigation position of nose-to-ceiling head position is more effective than the nose-to-floor position in delivering a 120-mL irrigation to the sphenoid sinuses [42].

### 6.2. Intranasal corticosteroids: standard delivery (drops and sprays)

In the management of CRSwNP, the use of topical corticosteroids have keystone role. Intranasal corticosteroids (sprays or drops) are recommended before or after the surgery for CRSwNP. The use of INCS as sprays or drops have noteworthy benefits. Its advantages include improved symptoms, endoscopic views, size of polyp, quality of life, objective tests of smell, airway, and polyp relaps. Headache, epistaxis, and nasal mucosal damage may be seen as side effects [23, 40, 41, 43].

### 6.3. Intranasal corticosteroids: nonstandard delivery (irrigation and nebulizers)

Nonstandard topical corticosteroid delivery system, especially after sinus surgery, is an option in CRSwNP. General benefits are not available to statistically approve therapeutic recovery on existing evidence. Although evidence of adrenal suppression has not been seen, this cannot be ruled out by nonstandard delivery and dosing regimens. They have off-label use and possible minor side effects in comparison with oral corticosteroids [23].

### 6.4. Oral corticosteroids

The short-term oral corticosteroids usage in treatment of CRSwNP is strongly recommended. Both in subjective and objective measurements, this treatment provides a considerable short-term healing in the patients with CRSwNP. Patients must be prescribed systemic corticosteroids in acute aggravations of CRSwNP. The recovery time may take 8–12 weeks with the use of INCS. Further gastrointestinal complications may also be seen. There may be temporary adrenal inhibition, insomnia, and elevated bone turnover. With long-term management, the entire well-known corticosteroid complications may be seen. Corticosteroid agents have significant benefits over harm in short-term usage. The use of corticosteroids in long term or frequently is not encouraged by the literature and has further risk of damage to the patients [10, 33, 37, 40, 43].

### 6.5. Antibiotics

#### *6.5.1. Oral out of macrolide antibiotics for <3 weeks*

In general, there is no recommendation to prescribe nonmacrolide antibiotics less than 3 weeks course for the patients with nonacute clinic conditions of CrSWNP. Oral doxycycline therapy for 3 weeks decreases the polyp size and postnasal discharge, but this therapy cannot decrease the other complaints in patients with CRSwNP compared to the placebo. Because there is no placebo in the erdosteine study, it is impractical to establish a benefit. There may have gastrointestinal discomfort and risk of resistance and anaphylaxis. There may be more harm than benefits [10, 23, 40].

#### *6.5.2. Oral out of macrolide antibiotics for >3 weeks*

Long-term oral nonmacrolide antibiotics for more than 3 weeks course in the management of adult chronic rhinosinusitis with nasal polyp (CRSwNP) is not currently recommended [10, 23].

#### *6.5.3. Macrolide antibiotics*

Macrolides may have advantageous effects after endoscopic sinus surgery to reduce polyp recurrence and recover symptoms of CRSwNP. Benefits have shown outweigh harm. They may have considerable drug interactions. Also, they may cause infrequent but serious cardiovascular complications [10, 23].

#### *6.5.4. Topical antibiotics*

Topical antibiotic agents have efficiency in just lower stage studies and have unidentified systemic absorption and side-effect scale. So, they should be prescribed only if conventional management modalities (oral antibiotics, steroid sprays, saline) are unsuccessful [10, 23].

### 6.6. Antifungals

#### *6.6.1. Oral antifungals*

For the treatment of CRSwNP, there is no recommendation for prescribing oral antifungal agents. Liver function tests may be deteriorated during systemic usage. Because there is a lack of evidence for the use of oral antifungal therapy, there is a greater risk of adverse effects than potential advantages. For the usual management of CRSwNP, clinicians should not prescribe the oral antifungal drugs [10, 23].

#### *6.6.2. Intranasal antifungals*

For the usual CRSwNP treatment, topical antifungal medications should not be utilized. In the management of typical CRSWNP, there is no benefit of topical antifungals, but there may be some benefits in some CRSwNP subdivisions, such as allergic fungal sinusitis. Because they have unconfirmed systemic absorption and side-effect scale, topical antifungal agents should only be considered if routine treatment modalities failed [10, 23, 41].

### 6.7. Anti-LT therapy

For patients with CRSwNP, montelukast may be useful and an option to substitute or supplement to INCS. Symptoms can be improved when compared to the INCS and may have limited benefits in addition to the INCS. Montelukast is in association with infrequent neuropsychiatric side effects in post-sale records. In addition, there has been also in association with high liver enzymes and Zileuton and other medications [23]. On the contrary, anti-leukotriene treatment is not supported for the patients with CRSwNP and this treatment modality is not recommended [10, 23].

### 6.8. Aspirin desensitization

This therapy must be considered and recommended in patients with aspirin exacerbated rhinitis disease to impede postoperative nasal polyp renewal. The aggregated grade of evidence is B. Benefits include decreased polyp reformation after surgery, decreased CRS symptoms in increased QoL and AERD, reduced the need for systemic corticosteroids, and decreased number of reoperations. It is necessary to be vigilant for gastrointestinal bleeding. It should be noted that this treatment has the potential to increase morbidity in patients with kidney disease and blood clotting problems with the increasing doses. There has been lower than 3% gastrointestinal complaints throughout the low-dose treatments. Absolute benefit is present rather than harm. Aspirin desensitization is a unique treatment modality for aspirin-sensitive patients with CRSwNP [10, 23].

### 6.9. Immunotherapy

For postoperative period of AFRS patients, this treatment modality offers an option with balanced benefit and harm. There is a limited data and the grade of evidence is C. If a patient represents enhanced sensitivity to the certain antigens, immunotherapy may be used to diminish the inflammatory load [23, 40].

### 6.10. Anti-IL 4 and anti-IL13 treatment

An anti-IL-4/13α subunit receptor antibody, dupilumab, has been approved for atopic dermatitis [44]. Add-on therapy of dupilumab may have a role in nasal symptom relief for patients with uncontrolled persistent asthma and comorbid persistent allergic rhinitis [45]. It has been observed that for the patient with nasal polyp, addition of subcutaneous dupilumab to mometasone furoate nasal spray reduced endoscopic nasal polyp scores after treatment. More sophisticated studies are needed to evaluate for longer treatment duration and larger patient samples [46].

### 6.11. Anti-IL5

Reslizumab is an anti-IL5 mAb derived from human tissues and acts diminishing the amount of eosinophils both in tissue and blood. Anti-IL5 antibodies may have benefit in the management of CRSwNP patients [10].

Mepolizumab, FDA approved for severe eosinophilic asthma, is another anti-IL-5 human derived antibody that has been studied in patients with CRS. For the patients with recurrent nasal polyposis, who receiving topical corticosteroids and required surgery, mepolizumab treatment showed a huge reduction in the need for surgery and a huge improvement in symptoms than placebo [44, 47]. Also, there is a continued clinical trial of mepolizumab in the patients with CRSwNP refractory to medical and surgical therapy [48].

Benralizumab is another anti-IL5 molecule that could potentially have some benefits for inhibiting the IL-5 pathway in CRS [44].

### 6.12. Anti-IL13

Lebrikizumab did not substantially heal FEV1 in mild-to-moderate asthma patients by inhibiting IL-13 pathway. Inhibiting IL-13 in this patient population was not satisfactory to improve lung function [49].

Tralokinumab, an agent of anti-IL13, in severe asthma exacerbations, has not been considered as a key role for interleukin 13, and it was stated that Tralokinumab is unsuccessful for management of severe, uncontrolled asthma [50–52].

Anrukinzumab is a humanized anti-IL-13 monoclonal antibody, which acts to block the cytokine and prevent the activation of IL-13Rα1 and IL-13Rα2 [53, 54].

So far, there is no approved anti-IL13 treatment modality for the patients with CRwNP.

### 6.13. Anti IgE

Omalizumab is a human-derived anti-IgE monoclonal antibody that prevents binding of IgE to receptors on mast cells and basophils. Omalizumab has been approved for severe allergic asthma [44]. Anti-IgE therapy also reduces nasal polyp score in patients with severe comorbid asthma [55].

### 6.14. Intranasal triamcinolone acetonide/carboxymethylcellulose foam

For acute exacerbations of postoperative CRSwNP patients, it has been observed that topical triamcinolone acetonide/carboxymethylcellulose foam reduced systemic steroid need, is well tolerant, and a good treatment option [56].

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