

Aspirin-exacerbated respiratory disease and current treatment modalities

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Received: 12 July 2016 / Accepted: 16 August 2016
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Abstract Aspirin-exacerbated respiratory disease (AERD) refers to the combination of asthma, chronic rhinosinusitis with nasal polyposis, and acute upper and lower respiratory tract reactions to the ingestion of aspirin (acetylsalicylic acid, ASA) and other cyclooxygenase-1 inhibiting non-steroidal anti-inflammatory drugs. AERD affects 0.3–0.9 % of the general population. AERD generally occurs due to abnormalities in mediators and expression of arachidonic acid biosynthesis. Local IgE responses to staphylococcal enterotoxins may also be responsible for eosinophilic activation in the nasal polyp tissues of AERD patients. Clinical features of AERD include the onset of nasal congestion with anosmia, progressing to chronic pansinusitis and nasal polyps that regrow rapidly after surgery. Aspirin desensitization, Leukotriene-modifying agents, biologic agents, management of asthma, chronic

rhinosinusitis, and nasal polyposis are recommended as treatment modalities. Immunotherapy is prescribed only to those AERD patients who experience clear seasonal or perennial allergy symptoms in addition to the symptoms attributable to chronic nasal polyposis. There are also investigational and dietary therapies. In this review, the important aspects of AERD will be presented, along with a literature survey.

Keywords Aspirin-exacerbated respiratory disease (AERD) · Chronic rhinosinusitis with nasal polyposis · Asthma · Aspirin (acetylsalicylic acid, ASA) · Cyclooxygenase-1-inhibiting non-steroidal anti-inflammatory drugs

Definition

Aspirin-exacerbated respiratory disease (AERD) describes the combination of bronchial asthma, chronic rhinosinusitis (CRS) with nasal polyposis, and acute upper and lower respiratory system reactions to the intake of aspirin (acetylsalicylic acid, ASA), along with other cyclooxygenase-1 (COX-1)-inhibiting non-steroidal anti-inflammatory drugs (NSAIDs) [1]. AERD is characterized by hypersensitivity to aspirin, as well as non-selective inhibitors of cyclooxygenase (COX), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP) [2, 3]. Patients with AERD may also have aspirin-sensitive asthma or aspirin-intolerant asthma, though these terms only refer to one aspect of the dysfunction. The term “AERD” underlines the chronic upper and lower respiratory tract disorder as the main dysfunction, with a reaction to NSAIDs being an exacerbating situation [4, 5]; avoidance of NSAIDs among AERD patients does not lead to resolution of asthma or CRS.

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The first diagnosed case of aspirin hypersensitivity in a patient with bronchial asthma was reported in 1902, quite a while after clinical use of aspirin had begun. In 1968, Samter and Beers defined a triad, including asthma, nasal polyps, and aspirin sensitivity [4], that came to be called Samter's triad [1].

AERD describes the combination of:

- Asthma,
- Chronic rhinosinusitis (CRS) with nasal polyposis,
- Reactions to aspirin (acetylsalicylic acid, ASA) and other COX-1 inhibiting NSAIDs, in which the signs of nasal congestion and bronchoconstriction characteristically start 20 min to 3 h after intake [1].

Intake of aspirin, and the majority of other NSAIDs, leads to a range of upper and/or lower respiratory allergic reactions, consisting of rhinitis, conjunctivitis, laryngospasm, and bronchospasm [6, 7]. The upper and lower airways of those identified as having AERD share the same pathogenic manifestations, including intense eosinophilic infiltration and dysregulation of arachidonic acid metabolism. Local and/or systemic immune response(s) to staphylococcal enterotoxins have been suggested as a factor in the pathogenesis of CRSwNP in AERD patients [3, 8].

Epidemiology

AERD affects 0.3–0.9 % of the general population; however, the prevalence increases to 10–20 % among asthmatics and up to 30–40 % among asthmatics with nasal polyposis [9–13]. The prevalence of AERD is around 7 % among patients with asthma, according to a 2014 meta-analysis of clinical trial data [14]. Among patients with severe asthma, “the prevalence is twice as high, at approximately 14 %”. Among patients with nasal polyposis or chronic rhinosinusitis, “the prevalence is about 10 and 9 %, respectively” [1].

Symptom onset is both earlier and significantly more severe in females than males [13, 15]. Sex hormones might affect “both autoimmune responses and repair mechanisms”, and might explain the observed gender disparity [15].

Pathogenesis of AERD

AERD typically develops due to abnormalities in mediators and expression of arachidonic acid biosynthesis. Elevation of Cys-LT levels have been observed in the urine, sputum, peripheral blood, and exhaled breath of AERD patients following aspirin consumption [16]. Dysregulation

of arachidonic acid (AA) metabolism, “particularly with an overproduction of leukotrienes, originates from decreased inhibition of the 5-lipoxygenase (5-LO) pathway of the AA metabolic process by the prostaglandin E2 (PGE2)”. “The overproduction of leukotrienes is further exacerbated by the activity of cyclooxygenase-1 (COX-1) inhibitors (which block production of PGE2)”. Furthermore, patients with AERD may have decreased production of regulating fatty acid, including lipoxins [1].

Cysteinylleukotrienes (CysLTs) are highly effective pro-inflammatory mediators linked to airway inflammation, which stimulate “bronchoconstriction, eosinophilic inflammation, mucus hypersecretion, and increases in vascular permeability” [17]. Considerable increases in CysLT levels have been observed in CRSwNP sino-nasal tissues of AERD patients compared to aspirin-tolerant asthma (ATA) patients. Additionally, significant reductions in urinary leukotriene (LT) C4 levels have been observed following endoscopic sinus surgery to treat CRSwNP in AERD patients [18]. The primary cellular origin of leukotriene LTC4 in patients with AERD seems to be the bronchial mast cell, though eosinophils are also capable of producing large amounts [19]. Both cell types are more prevalent and stimulated in the respiratory tracts of patients with AERD [20–22].

Strong eosinophilic infiltration is a critical histological characteristic of CRSwNP in AERD patients, in contrast to patients with other forms of NPs [8]. AERD patients show elevated levels of inflammatory mediators, such as “CysLTs, ECP, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), eotaxin, and regulated on activation, normal T cells expressed and secreted (RANTES)”; these are all generated primarily by eosinophils [8, 23, 24]. Steinke et al [25] recently demonstrated that increased INF-gamma levels expressed by eosinophils in NP tissue distinguished AERD from chronic hyperplastic eosinophilic sinusitis.

Local IgE responses to “staphylococcal enterotoxins” may generate “eosinophilic activation in the NP tissues of AERD patients” [26, 27]. “Staphylococcal enterotoxins (acting as superantigens)” have been shown to activate “Th2 cells and trigger discharge of Th2 cytokines, such as IL-4, IL-5, and IL-13”. These types of events result in the development of eosinophilic inflammation, a characteristic of CRSwNP [28].

Diagnosis

History of an asthmatic episode following the intake of aspirin or another NSAID is indicative, and sometimes even diagnostic. Nevertheless, 16 % of individuals who believed they had AERD because of an asthmatic episode

following ingestion of aspirin/another NSAID did not experience problems with oral aspirin and, thus, did not meet conditions for AERD [29]. In similar research, among subjects who had nasal polyps, chronic sinusitis, and asthma, and were avoiding aspirin and NSAIDs, only 43 % had positive oral aspirin troubles [29]. Therefore, AERD is either excessively recognized (due to coincidental history) or under-diagnosed (because of the lack of previous contact with aspirin or a COX-1 inhibitor in the course of inflammatory respiratory system disease).

Aspirin challenge is the defacto standard for the verification of AERD [6, 7, 30]. There are four paths of provocation challenges: oral, bronchial inhalation, nasal inhalation, and intravenous [30–34].

Subjects with histories of asthmatic symptoms following the intake of aspirin or another non-selective COX inhibitor, or those with chronic rhinosinusitis, nasal polyps, and/or asthma, should be assumed to have AERD. Some sufferers have particular histories of uncomfortable side effects to non-selective COX inhibitors, pointing to the existence of AERD. CRSwNP is a particular feature of the upper respiratory tract of AERD patients [8, 35].

In vitro diagnosis of AERD is discussed in literature with some controversy [36]. In vitro tests which could distinguish aspirin-tolerant from aspirin-intolerant individuals are currently under investigation. Although a few studies demonstrate that aspirin triggers the release of LTC₄ from peripheral blood leukocytes (PBL), the differences between ASA-intolerant and ASA-tolerant subjects are only quantitative and not always reproducible. Similarly, basophil activation test based on cytofluorimetric measurement of surface CD63 or CD203c molecules upon stimulation with aspirin or other NSAIDs do not yield consistent results in discriminating AERD from ASA-tolerant asthmatics [37, 38]. Further in vitro tests including blood eosinophil levels, eosinophilic cationic protein testing, and sputum and nasal eosinophil counts can be measured, and are increased with symptom aggravation in AERD patients [39]. Most clinicians have some acquaintance of the use of in vitro tests. However, the underlying concepts pertaining to diagnostic tests in general, and to their use for diagnosis of a diseases in particular, are often less familiar, and perhaps less well understood. The current concepts point to the pathways of lipids (exemplified by eicosanoids) and other molecules related to them (e.g., cytokines, growth factors, cell surface markers, second messengers of cell signaling, enzymes and receptors) [36]. Eicosanoids, introduced in 1980 by Corey et al. [40], are oxygenated metabolites of the (5Z, 8Z, 11Z, 14Z)-5,8,11,14-eicosatetraenoic acid, widely known as arachidonic acid (AA). Arachidonic acid is the main source of the eicosanoid cascade in humans involving more than 50 enzymes generating a multiplicity of eicosanoids [41–43].

The COX- and 5-lipoxygenase (5LO-) pathways are intimately linked to AERD [36].

The defacto standard test is aspirin challenge, which is suggested for patients with bronchial asthma and CRSwNP [44]. Four ways of challenge may be used: oral, bronchial inhalation, nasal inhalation, and intravenous routes [2, 44, 45]. The oral challenge test, utilizing the Stevenson method, is usually used in the US [2]. The aspirin amount is elevated every 2–3 h for 72 h, starting with 30 mg and increasing to a collective dosage of 1000 mg; the forced expiratory volume level in 1 s (FEV₁) is assessed every 60 min throughout the challenge [2, 44]. The base FEV₁ should be at a minimum 1.5 l and over 70 % of the estimated value [2, 44]. The bronchial challenge evaluation is better and faster compared to the oral challenge test [44].

The nasal aspirin challenge test is advisable for subjects with contraindications to the use of oral or breathing assessments [44, 45]. Even though the nasal challenge evaluation is safe and helpful in identifying AERD—systemic symptoms and bronchospasms seldom develop [44]—“the sensitivity and negative predictive value are less than those of the other two tests” [44, 45]. An intravenous provocation test using NSAIDs can also be carried out [44]. Careful observation of subjects with asthma and rhinosinusitis is important. The possibilities of a positive oral aspirin challenge test are over 80 % in those with a medical history of reaction to NSAIDs, and increases to 90 % if several of these reactions are present [13].

In addition to provocation tests, imaging studies, including the ostio-meatal unit-computed tomography (CT) scan and the paranasal sinuses series, may be helpful to find or verify the existence of the disorder and evaluate the severity of CRSwNP [46]. A CT scan or a plain X-ray can show opacification of both sinuses in the majority of AERD individuals. Alternative diagnostic methods, such as rhinoscopy and nasal endoscopy, may be employed to detect CRSwNP [8]. Imaging studies are not sensitive for AERD. These studies show the opacification of sinuses and severity of CRSwNP. Whereas neither opacification of sinuses nor CRSwNP are not specific for AERD. Acoustic rhinomanometry can also be used to evaluate nasal blockage [35].

Clinical attributes of AERD

AERD has become identified as “Samter’s triad, aspirin caused bronchial asthma, aspirin susceptible bronchial asthma as well as aspirin hypersensitivity” [2, 6, 47]. Despite the fact that it was first defined in 1922 by Widall et al. [48], the pathophysiology of AERD is not fully understood, and is not the goal of this review; this said, two

reviews on this subject were lately authored by Stevenson [2, 7, 30].

Clinical features of AERD consist of the onset of nasal congestion with anosmia, progression to chronic pansinusitis, and nose polyps that re-grow quickly following surgery [4, 7]. Night-time nasal blockage along with exhaustion due to lack of sleep are common among those affected. Bronchial asthma may precede upper respiratory tract problems, or appear subsequently. CT or fundamental radiographs of the sinuses expose extensive opacification within nearly all AERD patients [7, 49]. Standard imaging of the sinuses confirms a diagnosis of AERD [16].

The first clinical characteristic of AERD of the upper respiratory tract is generally nose congestion, and appears “during the third decade of life, associated with hyposmia as well as chronic rhinorrhea; the disease progresses to chronic pansinusitis, followed by the appearance of nose polyps that grow back quickly despite repeated surgery” [35]. Additional symptoms consist of face tension, a postnasal drip, nasal relieve, purulence, anosmia, a persistent cough, headache, tooth ache, ear pressure, exhaustion along with sleep deprivation, and halitosis [35, 49].

CRSwNP within AERD sufferers progresses aggressively. The nasal passage becomes filled, and “polyps protrude anteriorly into the face or posteriorly into the nasopharynx” [35]. CRSwNP tissue displays an edematous and often eosinophilic mucosa [8]. The most important pathological characteristic of CRSwNP in AERD individuals is infiltration as well as activation associated with eosinophils, connected with the discharge of the contents of eosinophil granules, which include eosinophil cationic protein (ECP) and/or main fundamental proteins [8, 49].

Treatment

Management includes “guideline-based management of bronchial asthma and sinus disease”, “avoidance of COX-1 inhibitors” and, for some patients, “aspirin desensitization achieved with high-dose aspirin therapy”. Regardless, many patients have inadequately controlled symptoms and require multiple sinus surgeries [50].

Patient education and counseling to ensure avoidance of COX-1 inhibitors, along with the identification of well-tolerated alternative drugs, are essential to AERD management, along with medical and surgical procedures to address the underlying bronchial asthma and CRSwNP [51]. Highly selective COX-2 inhibitors, for example celecoxib, are very well tolerated options, and acetaminophen (in doses as high as 1000 mg) and meloxicam (as high as 15 mg) may also be well tolerated by AERD patients [51, 52].

Leukotriene-modifying agents

LTMA should be a part of any treatment course for AERD to deal with the actual dysregulation of leukotriene production, as well as to safeguard patients from severe reactions to accidental NSAID exposure. Both leukotriene-receptor antagonists (LTRAs) (e.g., montelukast, zafirlukast) [53–56] and inhibitors of leukotriene synthesis (e.g., zileuton) [57, 58] work well for AERD.

As a practical matter, most physicians choose “an oral LTRA (montelukast, zafirlukast) for initial therapy, as opposed to the 5-lipoxygenase (5-LO) inhibitor zileuton, as zileuton requires twice-daily administration and periodic monitoring of liver function, and has some potential for drug interactions”. If patients do not improve after using the LTRA for 4–6 days, then zileuton might be added or used as a replacement therapy. In a survey of patients with AERD, participants recognized zileuton as “very effective” more frequently than LTRAs [1, 59].

NSAID avoidance

Patients with AERD should avoid “all NSAIDs that hinder COX-1, unless they have been desensitized to aspirin”. Patients with AERD usually tolerate “other options to treat discomfort and/or inflammation, although very sensitive patients may only respond to greater doses of nonacetylated salicylates or acetaminophen, in which case the following are recommended” [1]:

- NSAIDs with very weak COX-1 inhibitory characteristics (e.g., nonacetylated salicylates, for instance, salsalate),
- Acetaminophen (at doses as high as 650 mg; 20 % of AERD patients will respond to a dosage of 1000 mg) [60],
- Highly selective COX-2 inhibitors (e.g., celecoxib) [61].

Aspirin desensitization

Almost all AERD patients can be effectively desensitized to aspirin (acetylsalicylic acidity, ASA). The mechanism by which ASA desensitization alters an individual’s reaction to NSAIDs is not completely understood. One theory proposes that “desensitization and subsequent daily aspirin treatment reduces interleukin-4 (IL-4)-caused expression of leukotrienes by inhibiting the transcription factor, signal transducer, and activator of transcription 6 (STAT-6)” [62, 63].

The indications for aspirin desensitization in AERD include the following [1]:

- Nasal polyposis that returns or becomes worse after surgery despite LTMA, nasal glucocorticoids, and other appropriate treatments,
- Inflammatory conditions requiring daily NSAID therapy (e.g., joint disease),
- Atherosclerotic heart/vascular disease requiring the antiplatelet effects of aspirin,
- Recurrent headaches or other conditions requiring the intermittent utilization of NSAIDs after other available choices have proven ineffective.

Patient specific optimal doses of aspirin cannot be predictable in Aspirin desensitization. Aspirin is recommended 1300 mg daily (usually 650 mg bid) for 1 month. If there is significant improvement in upper and lower airway symptoms, the dose is decreased by one tablet (325 mg) monthly to either 650 mg AM and 325 mg at night or ideally 325 mg bid [2, 64].

Daily aspirin therapy can help to eliminate lower and upper airway symptoms in patients with AERD, though the effects on rhinosinusitis symptoms are usually more dramatic than the effects on bronchial asthma. Of note, there are no data to indicate aspirin is beneficial in treating airway disease in patients with bronchial asthma and nasal polyposis without aspirin intolerance. The effectiveness of daily aspirin therapy in dealing with lower and upper airway disease in patients with AERD, and the dosage of aspirin in this setting, are reviewed in depth elsewhere [1].

Berges-Gimeno et al. [65] reported that in a group of 172 patients, who had undergone aspirin desensitization and treated with daily aspirin 650 mg twice daily for a year, 24 (14 %) discontinued ASA treatment due to known side effects (i.e. gastric pain or bleeding, non-gastrointestinal bleeding, such as epistaxis, and urticaria). Eleven percent of patients stopped due to poor response and other reasons (i.e. planned surgeries, rash, death from other causes, etc). Of the remaining 126 patients who were continued on aspirin for a year, 110 (87 %) benefitted from aspirin therapy [65].

Biologic agents

Omalizumab and mepolizumab have both been analyzed in treating patients with AERD [1].

Omalizumab: A small trial recommended that “omalizumab (an anti-immunoglobulin E [IgE] monoclonal antibody) might be useful in patients with nasal polyps” [66]. Twenty-four patients with CRS with nasal polyposis and concomitant bronchial asthma, roughly half of whom had AERD, received 4–8 subcutaneous doses of omalizumab ($n = 16$) or a placebo ($n = 8$), in line with omalizumab dosing recommendations for bronchial asthma (according to serum IgE level and the body mass) [66].

Omalizumab treatment was connected with enhanced airway signs and symptoms and improvements in general well being, with a substantial reduction in total endoscopic nasal polyposis scores after 16 days, in comparison with placebo. Alterations in polyposis scores were confirmed by way of sinus calculated tomography (CT) scoring (Lund–Mackay score), factoring in the existence of allergies.

However, within the subset of patients with AERD, improvements were not clearly observed on CTs. Thus, it is unclear whether this effect is particular to AERD. Moreover, Ta and White [59] reported that a minority of 190 AERD patients indicated that a combination of medications (aspirin, leukotriene receptor antagonist, zileuton, or omalizumab) was more effective than one alone. Despite ongoing medical therapy, the burden of disease in AERD remains high. Therefore, omalizumab may be used additionally to the other therapies.

Mepolizumab: Mepolizumab is “an anti-IL-5 monoclonal antibody that has been studied in patients with severe bronchial asthma and bloodstream or sputum eosinophilia”. In a small, randomized trial of patients with severe nasal polyposis refractory to glucocorticoid therapy, subjects received two doses of intravenous mepolizumab 4 weeks apart, or a placebo; the primary result measured was total polyp score, as evaluated by nasal endoscopy at 2 weeks [67]. Five of 20 patients within the mepolizumab arm were aspirin-intolerant, and 10 had bronchial asthma. After 2 weeks of treatment, 12 of 20 patients within the mepolizumab arm displayed a significant decrease in total polyp score, in comparison with one out of the placebo arm. Even though this study had significant restrictions, including a high overall dropout rate as well as an unclear number of patients with confirmed AERD, the outcomes indicate that eosinophil-specific treatments might be of some benefit for eosinophilic nasal polyposis, which is common in AERD. However, whether mepolizumab provides specific additional benefit in AERD beyond what can be predicted in the eosinophilic nature from the bronchial asthma and nasal polyps of AERD, continues to be unclear. IL-5 has a critical role in influencing the biological activities of eosinophils, therefore Mepolizumab, anti-IL-5 monoclonal antibody, and the receptor of IL-5 are a clear target in the treatment of hypereosinophilic diseases [68]. The spectrum of eosinophilic disorders is broad, and includes the hypereosinophilic syndrome (HES), nasal polyposis (NP), COPD with eosinophilic airway inflammation [69], allergic rhinitis, atopic dermatitis, eosinophilic esophagitis, eosinophilic granulomatosis with polyangiitis, but especially bronchial asthma [70]. AERD is not reported in this article, however, it may be said that in case of eosinophilic nasal polyposis, which is common in AERD [67], Mepolizumab may be recommended.

Managing chronic rhinosinusitis with nasal polyposis

Effective management of chronic rhinosinusitis is important, and may lead to improvements in asthmatic symptoms [71]. Topical anabolic steroids are very good at controlling signs and symptoms of rhinitis, and could decelerate the recurrence of nasal polyps. Antibiotics should be used whenever an infectious component is apparent. Although antileukotriene drugs (ALD) might also “alleviate signs and symptoms of chronic rhinosinusitis and improve nasal patency in AERD patients, they are not more efficient among ASA-tolerant patients” [72]. Surgical methods (polypectomy, functional endoscopic sinus surgical procedures, or ethmoidectomy) are often required to relieve signs and symptoms of chronic rhinosinusitis at certain stages of the disease, and also to remove polypoid tissue from sinuses. Assessments of the results of endoscopic surgery in “ASA-sensitive patients with chronic rhinosinusitis and ASA-tolerant controls” indicate that patients with the ASA triad responded less well to surgical intervention [73]. Because surgery has no effect on the actual inflammatory element of rhinosinusitis, treatment with topical anabolic steroids can also be necessary post-surgery. Antileukotrienes and/or chronic dental aspirin after desensitization can also be considered as follow-up treatments after surgery [38].

Patients with aspirin-exacerbated respiratory system disease (AERD) and chronic rhinosinusitis with nasal polyps (CRSwNP) are frequently considered to be resistant

to plain medical and surgical intervention. Failure rates of normal endoscopic sinus surgery among these people are considered to be up to 90 %. Complete sphenoidectomy, maxillary antrostomy, and endoscopic modified Lothrop procedure (EMLP) are effective within a significant majority of patients with AERD and CRSwNP [74].

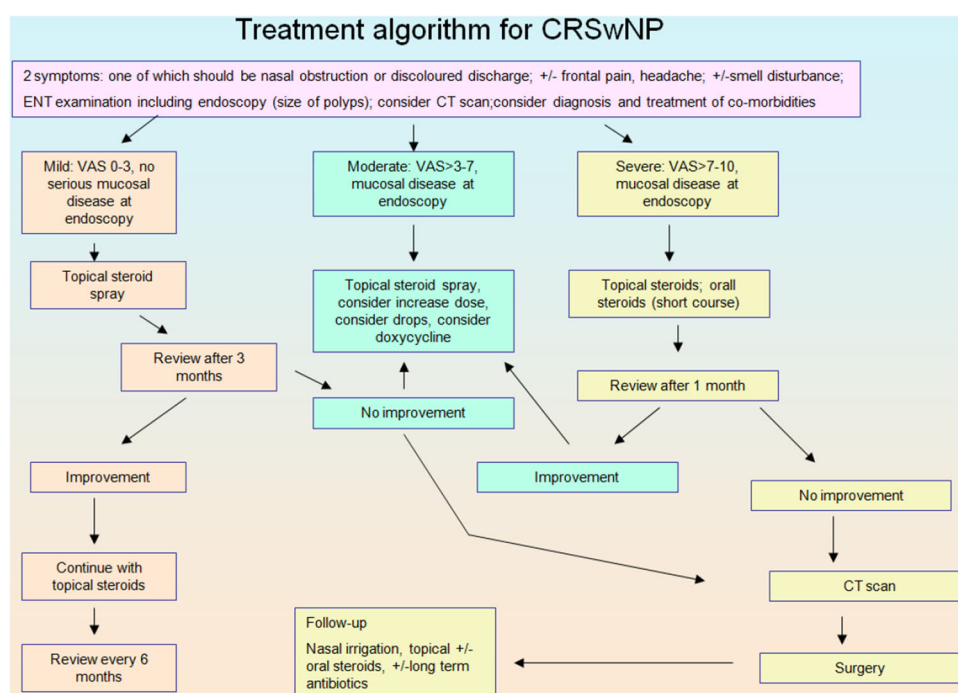
Treatment evidence and recommendations for CRSwNP [75] are shown on Fig. 1.

Management of bronchial asthma

Inhaled glucocorticosteroids in appropriate doses, frequently in conjunction with long-acting beta-2 agonists, are the best drugs for controlling asthmatic inflammation and bronchial asthma signs and symptoms in patients with AERD. In certain patients, chronic treatment with oral prednisone might be essential to control the condition. Inclusion of a leukotriene receptor antagonist, for example “montelukast, along with normal anti-inflammatory therapy (inhaled glucocorticosteroids, theophylline, short acting β_2 -agonists)” enhanced respiratory system function and alleviated clinical signs and symptoms within the 4-week treatment period in several aspirin-sensitive asthmatics [55].

In another study, 6 days of treatment with zileuton in patients with AERD resulted in improved lung function, even though the magnitude of improvement did not exceed that observed in ASA-tolerant patients in other studies [38, 58].

Fig. 1 Treatment evidence and recommendations for CRSwNP Prepared using European Position Paper on Rhinosinusitis and Nasal Polyps 2012 [75]



Immunotherapy

Ecological allergen immunotherapy is not suggested as the primary response to AERD, nor has it been formally investigated as a treatment for AERD. Prevalence rates of sensitization to ecological aeroallergens within the general human population are similar to those in patients with AERD; thus, many patients with AERD have co-morbid allergic rhinitis. Therefore, it may be ideal to prescribe allergen immunotherapy to individual AERD patients who experience obvious periodic or perennial allergic signs and symptoms in addition to their signs and symptoms of chronic nasal polyposis [50].

Investigational treatments

There are many ongoing studies of novel drugs to treat AERD, together with new agents that could show promise in AERD and eosinophilic nasal polyposis. “P2Y₁₂ is a G protein-combined receptor essential in platelet activation and aggregation. Thienopyridines, for example clopidogrel and prasugrel, are a type of selective P2Y₁₂ inhibitors utilized in acute coronary syndromes for antiplatelet activity. Both are recognized to decrease the introduction of platelet-leukocyte aggregates” [76].

At the tissue level, there is evidence that platelet-adherent leukocytes lead to inflammation in AERD [77]. Several studies in rodents indicate that platelets react to CysLTs, resulting in lung inflammation, which may be blunted by P2Y₁₂ antagonism [78, 79].

TP-receptor signaling may induce bronchoconstriction. In the murine type of AERD, both TP-receptor antagonism and genetic deletion of TP receptors avoided response to lysine aspirin challenge [80], indicating that TP antagonism may provide therapeutic benefit in humans. In addition, polymorphism from the thromboxane A₂ receptor (TBXA₂R) was connected with AERD within a Korean population [81].

Dupilumab, a completely humanized monoclonal antibody, which binds the alpha subunit from the IL-4 receptor and modulates signaling from the Th2 cytokines IL-4 and IL-13, continues to be investigated in a number of atopic illnesses, including eosinophilic bronchial asthma and atopic eczema [82, 83].

Nutritional interventions

Nutritional interventions to address the patient's dysregulated arachidonic acidity path are also of great interest in AERD. Because of the known contribution of acetylsalicylic acidity (aspirin) to pathognomonic respiratory system responses in AERD and many previously published reviews of salicylate responses in AERD patients [84, 85],

a minimal salicylic acidity diet was investigated as a therapeutic intervention. Sommer et al. [86] carried out a potential crossover study analyzing a minimal salicylate diet in ten patients with AERD. Nutritional sources of “salicylates, including many fruits, vegetables, herbal treatments, spices, herbs, walnuts, and many oils”, were removed from subjects' diets for 6 days. From the ten subjects who completed the study, both subjective symptom scores and physician endoscopic evaluation improved under the reduced salicylate diet in comparison with a regular diet [86]. A limitation of the study is that the outcomes measured were mainly subjective symptom scores.

Many fruits contain various amounts of salicylate—especially dried fruits and berries. Herbs and spices are also relatively high sources of dietary salicylates. Adherence to a low salicylate diet may be difficult for some due to the relative exclusion of many fruits, herbs, and spices. Conversely, eggs, grains, legumes, and meats, including fish, are generally considered to be devoid of significant amounts of salicylates. Most alcoholic beverages are a rich source of dietary salicylates; however, gin, vodka, whiskey, and brandy do not contain significant amounts [87, 88]. It is not easy to continue restrictive diet. According to Sommer et al. study [86], symptom scores improved by reduced salicylate diet. Mitchell et al [89] recommend that if dietary exclusion is considered, it should be preceded by a diagnostic diet for 6 weeks, followed by re-introduction of food to prove the efficacy of an exclusion of high salicylate foods.

Acknowledgments The preparation of this paper (including design and planning) was supported by the Continuous Education and Scientific Research Association.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This is a review, therefore there is no need for ethical approval.

Informed consent This is a review, therefore there is no need for Informed consent.

There is no funding source for this manuscript

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