HHS Public Access

Author manuscript

Int Forum Allergy Rhinol. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Int Forum Allergy Rhinol. 2016 December ; 6(12): 1273–1283. doi:10.1002/alr.21826.

Contemporary management of chronic rhinosinusitis with nasal polyposis in aspirin exacerbated respiratory disease: an evidence-based review with recommendations

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Abstract

Background—Chronic rhinosinusitis (CRS) in aspirin exacerbated respiratory disease (AERD) represents a recalcitrant form of sinonasal inflammation for which a multidisciplinary consensus on patient management has not been reached. Several medical interventions have been investigated, but a formal comprehensive evaluation of the evidence has never been performed. The purpose of this article is to provide an evidence-based approach for the multidisciplinary management of CRS in AERD.

Methods—A systematic review of the literature was performed and the guidelines for development of an evidence-based review with recommendations were followed. Study inclusion criteria included: adult population>18 years old; CRS based on published diagnostic criteria and a presumptive diagnosis of AERD. We focused on reporting higher-quality studies (level 2 or higher) when available, but reported lower-quality studies if the topic contained insufficient evidence. Treatment recommendations were based on American Academy of Otolaryngology

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Financial Disclosures: There are no relevant financial disclosures for Joshua M. Levy, Luke Rudmik, Anju Peters, Sarah Wise, or Brian Rotenberg.

Potential Conflicts of Interest: None to report.

guidelines, with defined grades of evidence and evaluation of research quality and risk/benefits associated with each treatment.

Results—This review identified and evaluated the literature on 3 treatment strategies for CRS in AERD: dietary salicylate avoidance, leukotriene modification and desensitization with daily aspirin therapy.

Conclusion—Based on the available evidence, dietary salicylate avoidance and leukotriene modifying drugs are options following appropriate treatment with nasal corticosteroids and saline irrigation. Desensitization with daily aspirin therapy is recommended following revision ESS.

MeSH Key Words

sinusitis; aspirin; respiratory track diseases; review; evidence-based practice; asthma

INTRODUCTION

Aspirin exacerbated respiratory disease (AERD) represents a challenging syndrome of adult-onset asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP) and non-IgE mediated hypersensitivity to cyclooxygenase-1 (COX-1) inhibitors, such as acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDS)[1-4]. First recognized by Widal et al. in 1922[5] and further described by Samter et al. in 1967[6], AERD is associated with a severe CRSwNP phenotype with increased preoperative inflammation and lower health related quality-of-life (HRQoL) relative to CRSwNP patients without aspirin sensitivity[7].

Among patients with CRSwNP, prevalence of AERD has been reported at 8-26%, with up to 40% developing aspirin sensitivity during the course of their disease[1,8-10]. Although, aspirin challenge represents the gold standard for diagnosis of AERD[11], understanding of the pathophysiology contributing to AERD remains incomplete. Previous study has demonstrated imbalanced prostaglandin (PG) and leukotriene (LT) pathways of eicosanoid metabolism in patients with AERD[12]. Increased LT activity is associated with over-expression of 5-lipoxygenase and leukotriene C4 synthase, with increased inflammatory cysteinyl leukotriene (cysLT) production both at baseline and in response to COX inhibition[13,14]. Likewise, studies have demonstrated decreased production of anti-inflammatory prostaglandin E_2 (PGE_2) and reduced expression of COX-2, an enzyme important in PGE_2 synthesis in nasal polyp tissue from patients with AERD[15,16]. These alterations in arachidonic acid metabolism are associated with increased mast cell activation and eosinophilic inflammation of the upper and lower airways[17].

Although medical therapy is the cornerstone of management for AERD, the refractory nature of CRSwNP with aspirin sensitivity makes endoscopic sinus surgery (ESS) an important adjunctive intervention to help optimize clinical outcomes. However, relative to CRSwNP patients without aspirin sensitivity, AERD patients demonstrate significantly increased rates of revision ESS and olfactory dysfunction 18-months following ESS[18], with 37% requiring revision surgery at 5-years and 89% at 10[19]. This evidence highlights the need to continue improving the quality of care for this challenging sub group of patients with CRSwNP and AERD.

The purpose of this review is to identify treatment strategies for CRSwNP patients with AERD and to promote an evidence-based approach to their use (Table 1). For each therapeutic strategy, this review provides a focused summary of the literature. When possible, recommendations are developed based on the supporting evidence and value judgments made by the authors[20]. This review is not intended to replace professional judgment; rather, it is meant to highlight the best available evidence to assist clinicians in developing an evidence-based approach to management of CRSwNP patients with AERD.

METHODS

The overall development of this manuscript was performed by following the published methodology for an evidence-based review with recommendations[20]. We defined clinical management as inclusive of all testing, medical and procedural interventions in the treatment of CRSwNP in AERD. Consensus treatment recommendations for topical steroids, saline irrigations, antibiotics, oral corticosteroids and ESS were accepted[21], with review focusing on adjuvant treatment strategies. A systematic review of the literature was completed according to PRISMA recommendations[22], and included Medline, EMBASE and Cochrane Review Databases up to December 20, 2015. A screening literature search, which was used to identify all management strategies in the treatment of CRSwNP in AERD, used the search string: “chronic sinusitis OR chronic rhinosinusitis OR CRS AND aspirin exacerbated respiratory disease OR AERD OR aspirin triad OR ASA triad OR aspirin induced asthma OR Samter’s triad.” The resulting 67 abstracts were evaluated and three treatment strategies were identified: dietary salicylate avoidance, leukotriene modification, and aspirin desensitization.

A second focused literature search for each identified strategy was performed using the above search string and each of the three treatment strategies (i.e., “dietary salicylate avoidance,” “leukotriene modification,” and “aspirin desensitization”), for a total of three additional searches. In addition, reference lists of all identified studies were examined and we contacted experts in this field of research to ensure all in-press studies were included. All abstracts were reviewed and the following study inclusion criteria were applied: adult population>18 years old; CRS based on published diagnostic criteria[21,23]; known or suspected AERD; and clearly defined clinical end-points. While aspirin provocation testing was preferred to confirm a diagnosis of AERD, clinical diagnoses were accepted for review[10]. Identified studies were critically evaluated and the level of evidence was applied based on reported research methodology[24]. We focused on reporting higher quality studies, (level 2 or higher), but reported lower-level studies if the topic contained insufficient evidence. Exclusion criteria included: non-English literature, pilot studies, basic science research, reviews and expert opinion.

After qualitative evaluation of each study, a summary was produced that includes the aggregate grade of evidence and recommendations based on the American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guideline Development Manual (Table 2)[25]. Treatment recommendations were made assuming prior appropriate medical care for CRSwNP, including topical intranasal corticosteroids and saline irrigations[26]. When there was only one study evaluating an identified treatment strategy for CRSwNP in AERD,

an aggregate grade of evidence was not provided because grades are derived from the findings of multiple studies. Two authors (J.L. and L.R.) reviewed the literature and produced the initial manuscript. One at a time, subsequent authors (A.P., S.W., B.R.) were asked to review and critically appraise the recommendations based on the literature, following the previously described online iterative process of review and recommendation[20]. Recommendations incorporate the quality of research methodology, costs and the balance of benefit versus harm.

Results: Contemporary management of chronic rhinosinusitis in aspirin exacerbated respiratory disease

Dietary salicylate avoidance

Intolerance to ASA and other NSAIDs is a hallmark of AERD, with consensus recommendations to avoid selective COX-1 inhibitors in patients with AERD and uncontrolled asthma[27]. However, respiratory inflammation persists despite NSAID avoidance, with dietary non-acetylated salicylates representing a potential source of clinically relevant exposure[28]. Non-acetylated salicylates have been shown to selectively inhibit expression of the COX-2 enzyme, which is under-expressed in sinonasal polyps in patients with AERD[29,30]. Although, there is mixed evidence pertaining to the safety of selective COX-2 inhibitors in AERD[31-33], there has been an association between dietary salicylates and exacerbation of airway inflammation with asthma[34].

Dietary salicylates are found in various sources, with greatest concentration in dried fruits, berries, herbs, spices and many alcoholic beverages[35]. Dietary intake represents a significant source of salicylate exposure, with a systematic review by Wood et al. concluding that each person consumes an average of 3.16-4.42 mg of dietary salicylates each day[35]. Notably, salicylate concentration is variably reported in many dietary sources, likely due to variations in geographic origin and harvesting methods[36,37].

This review identified 1 randomized controlled trial (RCT) evaluating dietary salicylate avoidance for maintenance of CRSwNP in AERD[28]Table 3). One RCT was excluded from analysis as it represents a pilot study with collected data presented in the above mentioned, included trial[30]. Sommer at al[28] utilized a RCT with internal crossover design (level 2) to evaluate the effects of a 6-week low-salicylate diet on HRQoL and objective measures of sinonasal inflammation. Aspirin provocation testing was not required for study participation, with inclusion of 30 subjects with presumptive AERD. All patients continued their maintenance topical steroids and nasal irrigations during the study period. When compared to either baseline or an uncontrolled diet, dietary salicylate avoidance was associated with statistically significant improvements in multiple sinonasal (SNOT-22, Nasal sinus symptom scale) and asthma (Asthma control questionnaire-7) HRQoL scales. Significant improvements in physician-rated sinonasal inflammation using two endoscopic scoring systems, the Perioperative Sinus Endoscopy score and Lund-Kennedy Endoscopic Score[28], were also seen without controlling for operative status.

Summary: Dietary salicylate avoidance

Aggregate quality of evidence

N/A (Level 1: 0 studies; Level 2: 1 study – inclusion of single study prevents aggregate summary)

Benefit

Improved HRQoL and objective sinonasal inflammation at 6-weeks.

Harm

Potential for incomplete dietary requirements with long-term utilization.

Cost

Low, may increase with dietitian consultation.

Benefits-Harm assessment

Preponderance of benefit over harm.

Value judgments

Additional studies are needed with larger sample sizes and longer time-horizon to improve the level of evidence and determine longitudinal stability of intervention; however the low cost, ease of adoption, and a preponderance of benefit over harm all favor option.

Recommendation level

Option.

Intervention

Dietary salicylate avoidance may be considered as an adjunctive treatment among patients with AERD and sinonasal symptoms not controlled by topical corticosteroids or sinonasal irrigations.

Leukotriene modification

Leukotrienes are effectors of early- and late-phase inflammation, and represent the primary mediators of aspirin hypersensitivity in AERD[11,38]. Cysteinyl leukotrienes (cysLTs) are found in mast cells and other inflammatory cells, with increased production among patients with AERD[39]. The benefits of leukotriene blockade on symptoms of CRSwNP were first anecdotally reported by asthmatic patients with nasal polyposis. Subsequently in 1999, Parnes et al. prospectively examined the effects of leukotriene modifying drugs (LTMDs; synthesis inhibitor zileuton and receptor antagonist zafirlukast) in patients with CRSwNP, reporting improved symptoms with decreased polyp burden and oral steroid utilization[40].

LTMDs pharmacologically disrupt the production and activity of inflammatory mediators created by aspirin and other NSAIDs, which shunt arachidonic acid metabolism from anti-inflammatory PG to LO pathways, with subsequent generation of cysLTs and other pro-

inflammatory mediators[12]. LO pathways represent an attractive pharmacologic target for AERD, as patients have increased expression of cysLT receptors, with increased production of cysLTs both at baseline and in response to aspirin provocation[4,14,41].

LTMDs inhibit cysLT activity via two separate mechanisms: inhibition of cysLT synthesis or blockage of cysLT activity. The medications montelukast and zafirlukast function as inhibitors of the cysLT receptor 1 (cysLTR1), thereby blocking the downstream effects of cysLTs. Found in nasal mucosal inflammatory cells, peripheral leukocytes and airway smooth muscle, the expression of cysLTR1 is increased in patients with AERD, with decreasing levels following aspirin desensitization[14,42]. Leukotriene receptor antagonists are indicated for asthma maintenance treatment, as well as prophylaxis of exercise-induced bronchospasm and allergic or perennial rhinitis[43,44]. Zileuton prevents the synthesis of cysLTs by inhibiting the 5-lipoxygenase (5-LO) enzyme, and is indicated for the prophylaxis and chronic maintenance of asthma. First introduced in the United States in 1996[45], zileuton is proposed to have increased efficacy for sinonasal symptoms in patients with AERD, but requires clinical monitoring secondary to self-limited hepatic toxicity in 4.4%[41,46].

Both families of LTMDs have been associated with adverse reactions, with a 2008 report by the U.S. Food and Drug Administration warning of an increased risk of neuropsychiatric events associated with the use of antileukotriene agents[47]. Perona et al. retrospectively reviewed individual case safety reports in the World Health Organization's VigiBase for reports of psychiatric disorders associated with montelukast, finding that neuropsychiatric side-effects were more frequently reported in children than adults, with sleep disturbances, depression/anxiety and psychotic reactions. Suicidal behavior and completed suicide were more frequently reported than previously thought in practice, and occur most commonly in adolescents[48].

This review identified 3 randomized controlled trials (RCTs)[49-51] evaluating the impact of LTMDs on symptoms of CRSwNP in AERD (Table 4). Two observational cohort studies and two case series were excluded from analysis due to a low level of evidence[52-55]. Additionally, a systematic review and meta-analysis[56] (level 1) was excluded as AERD was infrequently reported and was not independently analyzed for sinonasal outcomes.

A RCT by Schäper et al .[51] (level 2) evaluated the effects of montelukast on 24 patients with CRSwNP and mild to moderate asthma, with or without aspirin sensitivity. The study included a six-week trial of montelukast with a blinded, crossover design, finding that leukotriene blockade is associated with significant improvements in rhinoscopy, sinonasal symptoms and nasal airflow among CRSwNP patients. Nasal lavage demonstrated significant reduction in eosinophil concentration and inflammatory mediators compared to baseline and control. Comorbid aspirin sensitivity was not found to influence results.

Two additional RCTs (level 2) evaluated the role of zileuton for treatment of CRSwNP in AERD. Dahlén et al.[50] examined the effects of adding zileuton to maintenance oral and inhaled corticosteroids for patients with aspirin intolerant asthma (AIA), reporting improved nasal symptoms, nasal airflow and subjective sense of smell following 6-weeks of therapy. Results were not controlled for concurrent oral or intranasal corticosteroids, which were

respectively utilized in 35% and 53% of subjects. Fischer et al.[49] treated previously diagnosed AERD patients with zileuton for 1 week prior to aspirin challenge, finding decreased nasal symptoms and mast cell mediators relative to placebo without an associated decrease in the diagnostic sensitivity of aspirin provocation for AERD. Head-to-head evaluation of montelukast versus zileuton for the control of CRSwNP symptoms in AERD has not been previously evaluated with a high level of evidence, nor has the efficacy of combined LTMD therapy.

Summary: Leukotriene modification

Aggregate quality of evidence

B (Level 1: 0 studies; Level 2: 3 studies)

Benefit

Improved sinonasal symptoms, subjective sense of smell and nasal airflow among patients with AERD following 6-weeks of therapy with either montelukast or zileuton. Secondary benefit of decreased airway symptoms following aspirin provocation testing among patients with suspected AERD without an associated decrease in diagnostic sensitivity.

Harm

Potential gastrointestinal and sleep disturbances, increased bleeding risk and risk of eosinophilic granulomatosis with polyangiitis (Churg-strauss syndrome). Potential neuropsychiatric events including completed suicide. Zileuton associated with self-limited hepatic injury in 4.4%.

Cost

Moderate, drug costs and lab monitoring with zileuton (Table 5).

Benefits-Harm assessment

Balance of benefit and harm.

Value judgments

Recommendations tempered by clearly defined adverse reactions without defined improvement in sinonasal HRQoL. Additional study is needed to further determine effect on patient-centered outcomes and longitudinal stability of intervention.

Recommendation level

Option.

Intervention

Trial of LTMD may be considered for persistent symptoms of CRSwNP in AERD not controlled by topical corticosteroids or sinonasal irrigations.

Desensitization with daily aspirin therapy

The process of desensitization begins with a provocative aspirin challenge, followed by repeated exposures of increasing dosage until a threshold is reached[8,57,58]. Following threshold exposure, a dose-continuation phase is utilized to maintain tolerance, typically with daily doses of oral aspirin[12,59]. While per oral application is considered the standard approach, various protocols have been described, with endonasal, bronchial, and intravenous routes of aspirin exposure[58,60]. Despite variation in specific protocol, the majority of challenges occur over 24-48 hours and are completed under close clinical supervision[57].

The immunologic mechanisms associated with aspirin desensitization remain poorly understood, with clinical benefits extending beyond those seen with strict ASA avoidance[61]. AERD is associated with a physiologic imbalance in eicosanoid metabolism, with overexpression of inflammatory cysteinyl leukotrienes and associated mast cell receptors[13,14]. Desensitization is associated with reduction of these inflammatory mediators, with a suggested mechanism involving inhibition the IL-4 activated STAT6 pathway[62,63]. Elevated COX-1 and COX-2 activity has also been described, with increased expression of anti-inflammatory prostaglandins[61].

Desensitization followed by daily aspirin therapy has received a consensus recommendation for the treatment of CRSwNP in AERD by the Joint Task Force on Practice Parameters, representing several allergy and immunology governing bodies[64]. However, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) recommends ASA desensitization only in the setting of research oriented clinical trials[65]. Economic modeling has found ambulatory desensitization for AERD to represent a cost effective treatment, with an associated cost of $6,768 per quality-adjusted life year gained ($18.54 per additional symptom-free day)[66].

Indications for desensitization include positive provocation testing and intractable nasal symptoms and/or asthma despite appropriate medical therapies[67], as well as AERD patients requiring revision ESS or COX-1 inhibitors for cardiovascular protection[68]. It has been recommended that patients undergoing ESS complete desensitization 2-12 weeks following surgery, but consensus has not been reached[57,58,61]. Contraindications to desensitization have not been universally defined, but generally include pregnancy, unstable asthma, anticoagulation therapy, bleeding disorders and gastric ulcers[57,58,61].

Aspirin desensitization is associated with acute respiratory and systemic inflammatory reactions, and should only be completed in a monitored clinical setting.[58] The most common responses include cutaneous reactions and urticaria, but angioedema and anaphylaxis have also been described[58]. Reported adverse events associated with chronic aspirin therapy for AERD are predominately minor, with 8-23% of patients experiencing dyspepsia or epistaxis. Among the trials included in this review, there are no reports of major adverse events or gastrointestinal bleeding[69-75], with the longest follow-up of 36 months[73]. Follow-up of >30 months after desensitization has been evaluated by Comert et al.[76] and Cho et al.[77] (level 4), with no major adverse events associated with prolonged aspirin therapy. Berges-Gimeno et al.[78] (level 4) report two cases of gastrointestinal bleeding attributed to gastritis among 172 AERD patients receiving daily aspirin therapy, but no major adverse events or upper

gastrointestinal hemorrhage. Finally, Hoyte et al.[79] (level 5) reports three cases of pancreatitis associated with desensitization and daily aspirin therapy. However, this letter to the editor was not peer reviewed, with subsequent comments questioning this association among the identified patients[80]. Acquired tolerance is lost after 48-72 hours without maintenance aspirin, with an increased risk of life-threatening pseudo-allergic reactions with subsequent exposure[81]. It is therefore recommended that patients missing maintenance doses over 48 hours undergo a second oral challenge and desensitization under close clinical monitoring[84].

This review identified 1 systematic review[82] and 7 randomized controlled trials (RCTs)[69-75] evaluating the impact of aspirin desensitization on symptoms of CRSwNP in AERD (Table 6). Three cohort studies[59,83,84] and twelve case series[76-78,85-93] were excluded from analysis due to a low level of evidence. The highest quality study by Xu et al.[82] (level 1) included a systematic review of aspirin desensitization for the treatment of AERD, including several lower quality studies excluded from this current review[78,84-88,90,93]. Findings included the need for further high-quality studies, with reported improvements in non-validated nasal symptom scores, decreased endoscopic polyp scores, rate of revision ESS, CRSwNP exacerbations and intranasal or systemic corticosteroid utilization. The current review includes four RCTs that were not included in this study[69,73-75].

The RCT (level 2) by Fruth et al.[73] evaluated patients undergoing staged desensitization and 100mg. daily aspirin therapy 6-weeks following ESS. This represents the first placebo controlled RCT evaluating the effectiveness of low-dose aspirin therapy following desensitization. Significantly higher HRQoL and decreased rate of polyp recurrence was reported 36-months following intervention versus control subjects receiving daily placebo following ESS and desensitization. No adverse events associated with aspirin therapy were reported. Rozsasi et al.[72] compared 100mg. versus 300mg. aspirin for maintenance therapy of patients with a history of prior ESS, reporting an improved endoscopic polyp score with significant reduction in revision ESS and improved olfaction following 12-months of maintenance therapy with the higher, 300mg dose.

Several RCTs (level 2) reported desensitization outcomes without controlling for prior ESS. Świerczyńska-Krępa et al.[74] evaluated the effectiveness of daily oral aspirin among patients with AERD versus aspirin tolerant asthma (ATA), finding improved HRQoL and nasal symptoms among AERD patients, but not ATA or placebo controls. Esmaeilzadeh et al.[75] reported improved HRQoL and sinonasal opacification 6-months following desensitization with oral maintenance therapy, without a difference in several serum cytokines. Stevenson et al.[69] reported improvement in nasal symptoms and subjective sense of smell with decreased nasal steroid utilization following desensitization with oral maintenance therapy, while Parikh et al.[70] did not detect clinical improvements following desensitization and maintenance therapy with intranasal lysine-aspirin. Lee et al. [82] evaluated the comparative effectiveness of different doses of daily aspirin following desensitization, without comparison to control.

Summary: Aspirin desensitization for CRSwNP in AERD

Aggregate quality of evidence

B (Level 1: 1 study; Level 2: 7 studies-heterogeneity of methods and outcomes prevent A)

Benefit

Improved sinonasal HRQoL following ESS with reduced incidence of polyp recurrence, revision ESS, corticosteroid utilization and objective measures of olfaction.

Harm

Well defined risks associated with both desensitization and chronic aspirin therapy. Acute reactions occur in 8-23% of patients undergoing desensitization, and range from cutaneous flushing to anaphylaxis, with recommendation for completion of desensitization in a controlled medical environment. Chronic aspirin therapy is associated with dyspepsia, gastric ulcer formation and upper GI bleeding, with greatest risk among subjects with advanced age, taking higher doses of aspirin and concurrent corticosteroids.

Cost

Moderate to high 24 to 48-hour desensitization with protocols in ambulatory and inpatient settings. Low cost of daily aspirin therapy with total ambulatory cost estimates of $6,768 per quality-adjusted life year gained.

Benefits-Harm assessment

Balance of benefit and harm.

Value judgments

Desensitization with daily aspirin therapy represents a final option for the management of symptoms of CRSwNP in patients with recalcitrant disease despite appropriate medical and surgical therapies. Despite the high rates of disease recurrence following ESS, durable control of sinonasal inflammation can be obtained in a subset of subjects without desensitization, justifying the omission of desensitization prior to ESS. Additionally, the effectiveness of desensitization among patients with recurrent polyposis is understudied, with a single report demonstrating improved endoscopic scores among patients with active polypoid disease. The current evidence therefore does not support the utilization of desensitization prior to revision ESS.

Recommendation level

Recommendation following revision ESS.

Intervention

Desensitization with daily aspirin therapy should be offered as an adjunctive treatment for AERD patients with recalcitrant CRSwNP despite appropriate medical therapies, including dietary salicylate avoidance and LTMDs. Recommendation is limited to AERD patients undergoing revision ESS several weeks prior to desensitization.

Future Study

Omalizumab and the endoscopic modified Lothrop procedure (EMLP) represent emerging strategies for the treatment of CRSwNP in AERD. Omalizumab, a humanized recombinant monoclonal antibody that blocks immunoglobulin E activation of mast cells and basophils, is approved for the treatment of moderate to severe persistent asthma[94], with demonstration of efficacy in the treatment of CRSwNP.[95,96] The role of omalizumab in AERD was reported in a case series of 21 patients by Hayashi et al.[97] (level 4), demonstrating significantly improved nasal symptoms and corticosteroid utilization among 85.7% of patients 12-months following omalizumab.

The EMLP is an advanced surgical option for the treatment of recalcitrant frontal sinusitis. Creation of a common frontal “neo-ostium” allows increased penetration of topical corticosteroids,[98] with improved control of sinonasal inflammation[99]. Morrissey et al. report a retrospective cohort study (level 3) of patients undergoing EMLP, with subgroup analysis of 31 patients with AERD. Patients were followed for 36 months following EMLP, with 42% of AERD patients achieving control of sinonasal inflammation. An increased risk of recurrent nasal polyposis and revision EMLP was noted among AERD patients versus controls without aspirin sensitivity ($p<0.01$). Future study is necessary to further establish the roles of Omalizumab and the EMLP in the treatment of CRSwNP in AERD.

Overall Summary

Based on the best available evidence, an evidence-based treatment protocol for the management of CRSwNP in AERD would include the option of dietary salicylate avoidance and leukotriene modifying drugs for uncontrolled sinonasal and respiratory symptoms following appropriate treatment with intranasal steroids and saline irrigations. Desensitization with daily aspirin therapy recommended among a select group of AERD patients following revision ESS (Table 7).

CONCLUSION

This review evaluated the literature on three different treatment strategies for the management of CRSwNP in AERD using a specific protocol for the development of an evidence-based review with recommendations. An evidence-based treatment protocol for the management of CRSwNP in AERD would include an option for dietary salicylate avoidance and LTMDs following appropriate therapy with intranasal steroids and saline irrigations. A recommendation for desensitization with daily aspirin therapy is limited to AERD patients following revision sinus surgery. These evidence-based recommendations should not necessarily be applied to all AERD patients, and clinical judgment, in addition to available evidence, is critical to providing appropriate care.

Acknowledgments

Timothy L. Smith is supported by a grant from the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the National Institutes of Health, Bethesda, MD, USA (2R01 DC005805; PI/PD: TL Smith). Public clinical trial registration (www.clinicaltrials.gov) ID# NCT01332136.

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TABLE 1

Review Characteristics

Purpose	
•	Appraise the evidence evaluating treatment strategies for the management of CRSwNP in AERD
•	Promote an evidence-based strategy for management of CRSwNP in AERD
Goal	
•	Provide focused summaries and recommendations for treatment of CRSwNP in AERD in order to assist clinicians in optimizing patient management. CRSwNP in AERD is a heterogeneous disease for which effective management involves the expertise of multiple medical specialists. These evidence-based recommendations should not be dogmatically applied to all clinical situations, as multi-disciplinary collaboration and clinical judgment, in addition to the evidence, remain instrumental in determining the most appropriate care.
Focus	
•	Disease: Chronic rhinosinusitis with nasal polyposis in aspirin exacerbated respiratory disease
•	Population: Adults>18-years old
•	Intervention: Treatment strategies for CRSwNP in AERD
Intended Users	
•	Clinicians who care for patients with CRSwNP in AERD

TABLE 2

Recommendations based on defined grades of evidence*

Grade	Research Quality	Preponderance of benefit over harm	Balance of benefit and harm
A	Well designed RCT's	Strong recommendation	Option
B	RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies	Recommendation	Option
C	Observational studies (case control and cohort design)	Recommendation	Option
D	Expert opinion, Case reports, Reasoning from first principles	Option	No recommendation

*American Academy of Otolaryngology - Head and Neck Surgery Clinical Practice Guideline Development Manual, Third Edition[25].

TABLE 3

Summary of dietary salicylate avoidance for CRS in AERD

Study	Year	Study Design	LOE	Subjects (n)	Study Groups		Treatment Protocol	Primary clinical end-points		Conclusion
Sommer DD et al.[28]	2016	Randomized controlled trial with internal crossover	2	AERD *30	**1** **2**	Low salicylate diet; Regular diet	Dietary monitoring × 6 weeks	**1** **2**	HRQoL (SNOT-22, NSSS, ACQ-7); Objective (LKES, POSE)	Dietary salicylate avoidance is associated with improved HRQoL and validated measures of sinonasal inflammation.

ACQ-7 = Asthma Control Questionnaire-7; AERD = aspirin exacerbated respiratory disease; CRS = chronic rhinosinusitis; HRQoL = health related quality of life; LKES = Lund-Kennedy Endoscopic Score; LOE = level of evidence; NSSS = Nasal Sinus Symptom Scale; POSE = Perioperative Sinus Evaluation; SNOT- 22 = Sino-nasal Outcome Test-22.

*Presumptive AERD without oral aspirin challenge

TABLE 4

Summary of leukotriene modifying drugs for CRS in AERD

Study	Year	Study Design	LOE	Subjects (n)	Study Groups	Treatment Protocol	Primary clinical end-points	Conclusion
Fischer AR et al.[49]	1994	Randomized controlled trial with internal crossover	2	AERD 8	**1** Zileuton; **2** Placebo	600mg zileuton four times daily × 1 week prior to ASA challenge	**1** Symptoms	Zileuton is associated with improved nasal symptoms and decreased mast cell mediators following aspirin challenge.
Dahlén B et al.[50]	1998	Randomized controlled trial with internal crossover	2	AERD 40	**1** Zileuton; **2** Placebo	600mg zileuton four times daily × 6 weeks	**1** Symptoms; **2** Nasal airflow	Zileuton is associated with decreased nasal symptoms and increased nasal inspiratory airflow.
Schäper C et al.[51]	2011	Randomized controlled trial with internal crossover	2	AERD 12 ATA 12	**1** Montelukast; **2** Placebo	10mg montelukast daily × 6 weeks	**1** Symptoms; **2** Nasal airflow; **3** Endoscopy; **4** Olfactometry; **5** Nasal lavage	Montelukast is associated with improved symptoms, nasal airflow and inflammation among CRSwNP patients regardless of aspirin tolerance.

AERD = aspirin exacerbated respiratory disease; ATA = aspirin tolerant asthma; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyposis; LOE = level of evidence

TABLE 5

Estimated costs of leukotriene modifying drugs

Medication	Mechanism	Unit	Estimated market cost per unit ($)	Estimated cost per day ($)
Montelukast (Singulair)[43]	leukotriene receptor antagonist	30 tablets	214.99	7.16
Zafirlukast (Accolate)[44]	leukotriene receptor antagonist	60 tablets	181.45	6.05
Zileuton (Zyflo)[45]	5-lipoxygenase inhibitor	60 tablets	1755.99	117.07

TABLE 6

Summary of desensitization and daily aspirin therapy for CRS in AERD

Study	Year	Study Design	LOE	Subjects (n)	Study Groups	Treatment Protocol	Primary clinical end-points	Conclusion
Stevenson et al.[70]	1984	Randomized controlled trial with internal crossover	2	AERD 25	**1** DS with continued daily ASA; **2** DS followed by daily placebo	Ascriptin (325mg ASA + 150mg Maalox) daily × 3 months followed by washout × 1 month and re-DS with crossover	**1** Symptoms; **2** Disease control (oral/nasal corticosteroids)	DS with daily ASA is associated with significant improvements in nasal symptoms and reduced nasal steroid utilization.
Parikh et al.[71]	2005	Randomized controlled trial with internal crossover	2	AERD 22	**1** DS with continued nasal ASA **2** Placebo following DS	16 mg intranasal lysine-aspirin q48 hours × 6 months before crossover	**1** Endoscopy; **2** Symptoms; **3** Nasal airflow	Intranasal lysine-aspirin not associated with measurable improvement in patient symptoms or nasal inflammation.
Lee et al.[72]	2007	Randomized controlled trial	2	AERD 137	**1** DS with 325mg ASA bid; **2** DS with 650mg ASA bid	Maintenance ASA bid × 1 month, than adjusted and followed for 1 year	**1** Disease control (exacerbations, medicine use, ESS); **2** Symptoms	Maintenance ASA dosage has no influence on disease control, symptoms or ESS. 23% had adverse events or discontinued therapy.
Rozsasi et al.[73]	2008	Randomized controlled trial	2	AERD 14	**1** DS with 100mg ASA daily; **2** DS with 300mg ASA daily	Maintenance ASA daily × 24 months	**1** HRQoL; **2** Disease control (ESS) 3)Endoscopy; **3** Endoscopy; **4** Nasal airflow; **5** Olfaction; **6** Symptoms	DS with 300mg daily ASA associated with significant reduction in revision ESS with improved olfaction and nasal airflow.

Study	Year	Study Design	LOE	Subjects (n)	Study Groups	Treatment Protocol	Primary clinical end-points	Conclusion
Fruth et al.[74]	2013	Randomized controlled trial	2	AERD 70	**1** DS with daily ASA 6 weeks after ESS; **2** Placebo following DS	100mg ASA daily × 36 months	**1** HRQoL (RSDI); **2** Endoscopy; **3** Olfaction **4** Symptoms	DS with daily ASA is associated with decreased polyp recurrence and improved HRQoL, but not olfaction.
Świerczyńska-Krępa et al.[75]	2014	Randomized, controlled study with parallel- groups	2	AERD 20 ATA 14	**1** DS and daily ASA **2** DS and daily placebo	624mg ASA daily × 6 months	**1** HRQoL (SNOT-20) **2** Symptoms; **3** Maintenance therapy (nasal corticosteroid); **4** CT	DS with daily ASA is associated with significant improvements in HRQoL and nasal symptoms versus ATA and placebo.
Esmaeilzadeh et al.[76]	2015	Randomized, controlled study	2	AERD 34	**1** DS and daily ASA **2** Sham DS and daily placebo	625mg ASA twice daily × 1 month, then 325mg twice daily for 6 months	**1** HRQoL (SNOT-22); **2** Symptoms; **3** CT; **4** Cytokines	DS with daily ASA is associated with significant improvements in HRQoL and sinonasal opacification, but not cytokines IL-10, IFN-γ or TGF-β

AERD = aspirin exacerbated respiratory disease; ATA = aspirin tolerant asthma; CRS = chronic rhinosinusitis; CT = computed tomography; DS = desensitization; ESS = endoscopic sinus surgery; HRQoL = health-related quality of life; RSDI = rhinosinusitis disability index; LOE = level of evidence; SNOT-20 = Sinonasal Outcomes Test-20

Table 7

Summary of treatment recommendations for the management of CRS in AERD

Treatment strategy	Grade of evidence	Balance of benefit to harm	Recommendation level	Intervention protocol
Dietary salicylate avoidance	N/A	Benefit	Option	Trial of dietary salicylate avoidance may be considered for persistent sinonasal symptoms not controlled by topical corticosteroids or sinonasal irrigations.
Leukotriene modification	B	Equal	Option	Trial of LTMDs may be considered for persistent sinonasal symptoms not controlled by topical corticosteroids or sinonasal irrigations.
Desensitization with daily aspirin therapy	B	Benefit	Recommendation	Desensitization with daily aspirin therapy is recommended as an adjunctive treatment for AERD patients following revision ESS.

AERD = aspirin exacerbated respiratory disease; CRS = chronic rhinosinusitis; ESS = endoscopic sinus surgery; LTMD = leukotriene modifying drugs; N/A = not available.