



Updates on treatment options in aspirin exacerbated respiratory disease

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Purpose of review

The aim is to describe why this review is timely and relevant. Acetylsalicylic acid exacerbated respiratory disease (AERD) is a clinically significant disease affecting approximately 7% of all asthmatics or around 1,400,000 persons in the United States alone. A large portion of these patients remain undiagnosed. This review summarizes up to date knowledge on the pathophysiology, treatment opinions and provides an expert opinion on how to approach the AERD patient.

Recent findings

Findings describe the main themes in the literature covered by the article. Review of the current knowledge in terms of the key cells, cytokines/chemokines contributing to the acquired disease state of AERD. It also provides clinical approach toward the AERD patient with regards to current treatment options.

Summary

Summary describes the implications of the findings for clinical practice or research. This is an up-to-date review of the current literature, with insight into how to approach the management of an AERD patient.

Keywords

aspirin-exacerbated respiratory disease, aspirin-induced asthma, biologics, desensitization, nasal polyps

ACETYLSALICYLIC ACID (ASPIRIN/ASA) EXACERBATED RESPIRATORY DISEASE OVERVIEW

Acetylsalicylic acid (Aspirin/ASA) exacerbated respiratory disease (AERD) is a inflammatory disease of the upper and lower airways [1[¶],2]. Defining features: chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma, and an intolerance of cyclooxygenase 1 (COX1) inhibiting drugs [3,4]. The frequency is estimated around 7% of all asthmatic patients and 10% to 16% of nasal polypoid patients [5–7]. It commonly presents in the third to fourth decade of life, most have tobacco exposure in youth, and up to 50% describe a viral illness at the onset of symptoms [2,3,8]. Asthma, CRSwNP, and COX-1 intolerance rarely present at the same time and can present in any order [6,9]. Rhinitis (allergic or nonallergic) is the typical first manifestation and can be refractory to standard treatments, this progresses toward asthma, and worsening nasal congestion with diminished sense of smell coinciding with formation of polyps [6,9]. The presentation of polyps is when the intolerance of COX-1 drugs typically occurs [6]. AERD patients often require frequent antibiotics, systemic corticosteroids, surgeries, and have more emergency room and hospitalizations

because the inflammatory disease persists despite the avoidance of all NSAIDs [6,10]. Comparing patients with similar disease characteristic (asthma, CRSwNP) but Cox-1 tolerant, AERD patients have more severe and a harder to control disease course [8].

The AERD pathophysiology involves the dysregulated of arachidonic acid metabolism leading to altered lipid mediator production causing reduced prostaglandin E2 (PGE₂), elevation of cysteinyl leukotrienes (CysLTs), CysLT receptors, and prostaglandin D2 (PGD₂) [3,11,12]. An activated epithelial layer releases alarmins: IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). These alarmins then interact with cells of the innate immune cells and lead to more inflammation [1[¶],2,13]. Key cells of AERD dysregulation include the innate immune system eosinophils, basophils, mast cells and innate

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Curr Opin Allergy Clin Immunol 2022, 22:49–54

DOI:10.1097/ACI.0000000000000796

KEY POINTS

- AERD is an acquired disease of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and an intolerance of cyclooxygenase 1 (COX1) inhibiting drugs.
- AERD is relatively common in patients with asthma and nasal polyps.
- Key cells of AERD dysregulation include the innate immune system eosinophils, basophils, mast cells, platelets, innate lymphoid type 2 cells, as well as adaptive immune system B-cells producing IgE.
- Long term treatment of AERD involves intranasal corticosteroids, leukotriene inhibitors, aspirin desensitization and systemic biologics.

lymphoid type 2 cells, as well as adaptive immune system B-cells producing IgE [1[■],2,14,15].

Mast cells are elevated in nasal polyps and chronically activated in the airway tissue of AERD patients [1[■],16]. Dysregulation of the mast cells and function is key in the AERD disease state as well as the reactions observed with aspirin ingestion [13,17]. Mast cell dysregulation is linked with low PGE₂ and therefore a more active 5-lipoxygenase (5-LO) with higher leukotriene formation and feedback for more mast cell activation [17]. Activation of mast cells leads to a rise in tryptase, histamine and PGD₂ which is well documented during aspirin challenges [3,6,16,18].

In AERD, eosinophils are found in higher percentage in the upper and lower airway and nasal polyps compared to normal healthy controls. The eosinophils of AERD patients also release higher levels of lipid mediators, have higher adherence to platelets, are involved in fibrin formation and contribute to tissue remodeling and nasal polyps [1[■],15,19,20]. Eosinophils produce PGD₂, and cysteinyl leukotrienes like leukotriene c₄, Eosinophil development and proliferation is driven by IL-5 and movement is mediated by IL-4 and IL-13 [21,22,23[■]].

Innate lymphoid cells (ILC2) are T-cells that play a role in AERD, studies of patients during aspirin challenge had decrease peripheral ILC2 but elevated numbers in the nose. ILC2 produce IL-4, IL-5, IL-13 and lead to increase mucous and airway constriction, with increases in eosinophilia with triggers like allergens and viruses [1[■],24].

AERD patients have increased platelet leukocyte aggregates, and produce high amounts LTC₄ synthase, and IL33 compared to asthmatic and normal controls tolerant of Cox-1 drugs [1[■],2,13–15]. AERD platelets account for 50% of the peripheral blood granulocyte LTC₄ synthase, compared with aspirin

tolerant controls [14,15,20]. This elevation of LTC₄ synthase results higher thromboxane A₂ which contributes to bronchoconstriction [13]. The platelets can further this process by binding to leukocytes of the innate immune system leading to cysteinyl leukotriene overproduction, as well as increased 5-LO [13,14]. Elevated levels of LTC₄ have been found in the urine following aspirin challenges [14,25[■]].

The adaptive immune response likely plays a role as well due to B-cells and antibodies, specifically IgE. Patients with AERD have higher levels of IgE levels, with staphylococcus aureus antigens inducing IgE proliferation [17]. IgE will interact with the mast cells and basophils stimulating degranulation [1[■],17,26].

Recently, Stevens *et al.* compared patients with AERD and CRSwNP, there is evidence suggesting an increased role of basophils than had been previously considered [27]. Basophils are recruited through similar chemokines and cytokines as eosinophils [3].

Lower airway

For the treatment of lower airways, we follow the Global Initiative For Asthma 2021. Since much of the lower airway symptoms are driven by the upper airway, control of the upper airway is necessary. Much of the focus of this review is on the upper airway's CRSwNP.

Upper airway

The goal is threefold: treat chronic rhinosinusitis, treat their polyps and prevent polyp regrowth.

Topical steroids

Topical intranasal steroids are first line treatment for prevention of regrowth of nasal polyps and treating chronic rhinosinusitis. Over the counter topical steroid nose sprays fluticasone, budesonide nasal, beclomethasone dipropionate, are useful for allergic rhinitis and chronic rhinosinusitis but not approved for nasal polyposis [3]. Mometasone nasal is approved for nasal polyps at the higher dose 2 sprays each nostril twice daily, yet despite this in CRSwNP with AERD topical mometasone is frequently ineffective at preventing polyps from reforming as found in the 2020 San Nicolo *et al.* study [28]. This is likely because the paranasal sinuses do not get high amounts of steroids when delivered in this mechanism [29]. Therefore, we will use either budesonide ampules into a daily nasal rinse or if approved fluticasone exhalation delivery system (EDS-FLU) trade name Xhance. Both provide higher concentration of the steroid, higher up into the

sinuses and therefore more effective at treating polyps, but no head-to-head trials have been performed for these two treatment options [30,31]. The published reports on the efficacy of budesonide as a nasal rinse have variable efficacy, but generally effective [30,32–34]. This variability is likely due to the small number of studies, variable patient inclusion criteria, the amount of steroid used, and methods of performing the irrigation. Fluticasone exhalation delivery system has been approved in patients with chronic rhinosinusitis with and without polyps (CRSwNP/CRSwoNP) [31].

FUNCTIONAL ENDOSCOPIC SINUS SURGERY

AERD patients represent a subset of CRSwNP that have worse quality of life and require more frequent sinus surgeries due to the aggressive nature of the polyps. The purpose of surgery is to debulk nasal polyps and improve efficacy of medications such as topical corticosteroids. There is wide reported variability on recurrence of sinus surgeries due to polyps in AERD patients. Some AERD patient's polyps will reform as quickly as a few months after surgery [6,35]. More recent studies looking at CRSwNP and/or AERD patients noted 45–90% of them required recurrent surgery, some of this variability includes mixed population of patients (not just AERD patients), variable follow-up (18 months vs 5 years), and geographic variations [36,37]. A 2007 meta-analysis study found 40% of patients with CRSwNP had reoccurrence of polyps at 18 months but did not look at AERD specifically [38]. Two studies looked at AERD specific patients, Grose *et al.* found in a retrospective study probability of remaining free of revision surgery: 98.2% at one year, 78.8% at 3 years and 44.8% at 5 years. In that cohort 16 patients were also placed on monoclonal antibody therapy (omalizumab, mepolizumab, or both) [37]. One study showed a 5 year rate of polyp free symptoms of only 10% in AERD patients vs 84% CRSwNP but NSAID tolerant [36]. Surgery is helpful for debulking of nasal polyps but then patients require close follow-up for treatment options on prevention of polyp regrowth.

Leukotriene inhibitors

Proinflammatory cysteinyl leukotrienes (CysLT) specifically LTE₄, LTC₄, LTD₄ and their receptors CysLT_{1r}, CysLT_{2r}, CysLT_{3r} along with prostaglandin D₂ (PGD₂) play an important role in the disease state of AERD [1^o,2,15,27,39]. In AERD patients PGD₂ and CysLT are elevated in the blood and urine at homeostatic state, with activation of cysteinyl

leukotriene receptors leads to chronic inflammation granulocyte recruitment, vascular permeability and bronchoconstriction [1^o,2,11,15,40]. Some recent studies suggested use of CysLTs and PGD₂ levels as surrogate biomarkers to distinguish patients with CRSwNP and AERD, yet the significance and cut off levels remains debated [40]. There are two CysLT₁ receptor antagonist Montelukast, Zafirlukast [3,18] and the third is 5-lipoxygenase inhibitor, Zileuton. Montelukast is the best studied, and least expensive option, routinely given for AERD aspirin challenges. Zileuton was identified as helpful by patients in a survey by Ta and White [41]. It is a complimentary treatment in AERD patients to add a CysLT₁ receptor antagonist since it doesn't completely inhibit LT synthesis [3,6].

Aspirin desensitization

Aspirin desensitization is recognized as an effective long-term treatment with clinical benefit for those with AERD [42]. The pathophysiology of aspirin and why it's effective in this disease state is partially speculative by providing aspirin in high doses and over a long term it downregulates CysLTRs, STAT6 (a transcription factor in T₂ inflammation), IL4, and PGD₂ [3,13,16,25^o].

A review of 172 patients in the Scripps General Clinical Research Center (67%) experienced improvement after aspirin desensitization, patients who remained on the high dose aspirin for over a year 87% (110) had significant improvement in symptoms and assessment scores, with reduced steroid use and ER visits [4]. Since then more publications have discussed what therapeutic dose is required to maintain polyp remission as well as provide NSAID tolerance. In the authors opinion and prior publications support 50% of patients are successfully maintained on 1300 mg of aspirin daily initially lower to 650 daily with persistent polyp remission [25^o,43].

A recent European retrospective study published 2020 suggests aspirin desensitization may not always be the best treatment option in AERD. Laulajainen-Hongisto *et al.* described 171 patients split into treatment and control groups and compared aspirin discontinuation and frequency of corticosteroids [44]. They found that 63% of patients stopped aspirin therapy on average 2.1 years after the desensitization. Of those that did not continue on the aspirin treatment: 5 failed desensitization, 23 had symptoms (tinnitus, gastrointestinal pain, or worsening asthma), 28 (27.5%) said it did not work and 7 discontinued due to trauma or pregnancy [44]. Of the patients studied there were 37% of patients that remained on the treatment and found benefit. This

is contrasted with the 2003 and 2006 studies by Stevenson, Sweis *et al.* which showed aspirin failure rates of 13–23% [4,43–45]. For those patients that stop taking the aspirin daily, most common reasons being: GI pain or bleeding, anaphylaxis, sinonasal symptoms, epistaxis, nummular rash and asthma exacerbation [46]. A prior discussion has already been written about the discrepancies between these studies but in brief the variation in outcomes is attributed to much lower aspirin dosing, high rates of failed desensitization initially (perhaps due to protocol differences), side effects and comorbid complications [44,45].

Systemic corticosteroids

Due to its inflammatory etiology, asthma, allergic rhinosinusitis and eosinophilic polyps of AERD patients respond very well to systemic corticosteroids in terms of decreasing symptoms of polyps (improving sense of smell, nasal congestion and purulent drainage, improved lower airway symptoms). Unfortunately, steroids have a well-documented deleterious effect that is also cumulative including suppression of the hypothalamic pituitary and adrenal axis, osteoporosis, gastritis, weight gain, psychiatric changes including depression, anxiety, elevated sugars making in an inappropriate choice for daily use if avoidable.

Biologics

In the past decade, the monoclonal antibody therapy has become increasingly important in the treatment of AERD patients. All 5 of the available biological therapies could be used in AERD patients from the asthma standpoint, three of the available biologics also carry approval for nasal polyposis: Mepolizumab (anti-IL5), Omalizumab (anti IgE) and Dupilumab (anti IL-4 receptor and anti-IL13) [22,47,48]. The other 2 biologics are approved for asthma: Benralizumab (anti IL-5 receptor) and Reslizumab (anti IL-5). Out of these clinically dupilumab has had the greatest clinical success in our patients in treating the nasal polyps, chronic rhinosinusitis as well as asthma.

Mepolizumab has approval for severe asthma as well as CRSwNP [48]. A recent 2021 study by Buchheit *et al.* compared 18 AERD patients with 18 controls, both were on similar levels of aspirin daily therapy, zileuton, budesonide sinonasal irrigation and in the treatment arm placed on mepolizumab for average of 15 months, it translated to decrease in nasal polyp symptoms and improvement in upper and lower airway disease [49,50]. Interestingly, when used during aspirin challenges it was not

successful at preventing acute reactions to aspirin [2,51].

At the end of 2020, omalizumab was approved for treatment of nasal polyps, in addition to its asthma approval [47]. AERD patients have elevated IgE, with increased amounts in the sinuses and nasal polyps [1[¶]]. However, clinically omalizumab has not been as successful in obtaining control of the airway of AERD patients, so we do not frequently start it as the first biologic for an AERD patient unless there is another reason such as chronic spontaneous urticaria to initiate it.

Dupilumab an anti-IL-4 receptor alpha chain, blocking the downstream signaling of IL-4 and IL-13, has resulted in improved control of AERD patients who have severe sinopulmonary disease. This can be attributed to its treatment of two major cytokines and receptors of the type 2 inflammatory response. In a 5 patient case series of AERD patients who had previously failed aspirin challenges, all 5 tolerated increased amounts of aspirin compared to prior challenges with 3 out of the 5 having no symptoms up to 325mgs, 2 had symptoms at 162mg and the other at 325 mg. These findings suggest that dupilumab alone increases aspirin tolerance and could allow for some to use NSAIDs for analgesia, anti-inflammatory or anti-platelet therapy [21].

CONCLUSION AND AREAS OF FUTURE RESEARCH

In newly diagnosed AERD, we typically provide them with systemic corticosteroids and start either budesonide nasal rinses or Xhance, along with standard asthma treatment. For patients requiring frequent systemic corticosteroids, we place them on a leukotriene inhibitor and refer them to ENT colleagues to discuss surgical options with planned aspirin desensitization 4–6 weeks following. If they remain steroid dependent or have inadequate control despite nasal steroids, leukotriene inhibitors, high dose aspirin we add a monoclonal therapy. For patients whom aspirin desensitization and maintenance is otherwise contraindicated, or we will start biologic therapy sooner.

AERD affects approximately 1,400,000 people in the United States alone [5,52]. New understanding of the pathophysiology that led to the disease state also provides new treatment modalities. Future areas of research include understanding phenotypes of AERD and treatments for each. Additional gaps of knowledge include: cost benefit analysis on treatment options, as well as patient perceived benefit on the treatment options. Lingering questions remain if patients on biologic therapy can then use Cox1 inhibitors ad

lib, and if alcohol consumption can be liberalized when on treatments for AERD. Finally, a new biologic Tezepelumab, a human monoclonal antibody that inhibits the action of TSLP is on the horizon, targeting alarmins may be more relevant for AERD given that it is an acquired inflammatory disease.

Acknowledgements

None

Financial support and sponsorship

None

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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