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Update on Aspirin-Exacerbated Respiratory Disease

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Abstract Aspirin-exacerbated respiratory disease (AERD) is an acquired disease characterized by chronic eosinophilic airway inflammation with underlying dysregulation of arachidonic acid metabolism. The purpose of this paper is to review the latest developments in our understanding of the underlying pathophysiology including the role of eosinophils, mast cells, innate lymphoid cells (ILC_2), and platelets. Clinical features such as respiratory reactions induced by alcohol, aggressive nasal polyposis, and anosmia will allow for earlier recognition of these patients in clinical practice. The current state of the art management of AERD will be addressed including the ongoing central role for aspirin desensitization and high-dose aspirin therapy.

Keywords Aspirin-exacerbated respiratory disease (AERD) · Arachidonic acid · Prostaglandin E2 · Prostaglandin D2 · Aspirin desensitization

Introduction

Aspirin-exacerbated respiratory disease is an acquired disease characterized by chronic eosinophilic inflammation of the sinuses with or without asthma and pathognomonic respiratory reactions with exposure to all cyclo-oxygenase-1 (COX-1) inhibiting non-steroidal anti-inflammatory drugs (NSAIDs). The disease starts and continues in the absence of exposure to NSAIDs. The focus of this review is to highlight some of the recent discoveries in to the underlying mechanisms of the inflammatory process in AERD as well as the management. It is not meant to be a comprehensive review. Although much has been learned since the syndrome was first recognized in 1922, we still do not understand what is the underlying cause. As our understanding of the pathophysiology grows, new, targeted therapy options can be developed to better manage these patients.

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Overview of Aspirin-Exacerbated Respiratory Disease

Case reports of reactions to aspirin were published soon after the release of aspirin in 1899 by Bayer, with the first description of AERD in 1922 by Widal et al. in which they also reported on aspirin challenge and desensitization [1]. Although sinus disease is required for diagnosis, not all patients with AERD have asthma. Recently, there is an effort to change the name to NERD: NSAID-exacerbated respiratory disease but that nomenclature misses one of the more intriguing features of this disease in that high-dose aspirin therapy is an effective treatment [2, 3•]. None of the other NSAIDs have been shown to treat the disease.

Presentation AERD typically develops in the third or fourth decade of life in an individual with a history of a "head cold" that never went away with a progression to anosmia with chronic rhinosinusitis [4]. At some point in the clinical course, they can develop asthma. The severity of the asthma tends to correlate with the severity of the sinus disease. Although they previously tolerated COX-1-inhibiting NSAIDs, they are now sensitive with ingestion leading to severe respiratory symptoms within 30 min to 3 h from ingestion. If they have not taken aspirin or NSAIDs, AERD might not be recognized

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leading to a delay in diagnosis. The patient is slightly more likely to be a woman and to have had the need for multiple sinus surgeries.

The exact prevalence of AERD is difficult to determine. A recent meta-analysis found the prevalence of AERD was 7% in asthmatics with a rate doubling to 14% in patients with severe asthma [5•]. There is one interesting exception, which is that in China; the incidence of AERD is dramatically lower. Fan et al. performed aspirin challenges in 351 consecutive patients with chronic rhinosinusitis (309 of whom had nasal polyps) only two had a positive challenge (0.57%) [6]. This likely is due to the different inflammatory profiles: as the polyps in China tend to have more of a type 1 (TH1/TH17) inflammatory profile [7]. Some might argue that a 7–14% prevalence of AERD is higher than what is seen in clinical practice, but it may also reflect that in clinical practice, we may be missing these patients.

There are several features that may help identify patients with AERD earlier in the course of the disease. The first of which is sensitivity to alcohol. Over the years, we have had many AERD patients report respiratory reactions to alcohol that developed after they acquired AERD but had never looked at it closely. A questionnaire was developed to assess alcohol-induced respiratory symptoms in patients with aspirin-challenge-proven AERD compared with aspirin-tolerant asthmatics (ATA), aspirin-tolerant patients with CRS, aspirin-tolerant patients with nasal polyps (NP), and healthy controls [8]. Eighty-three percent of AERD subjects reported respiratory symptoms with the ingestion of alcohol (runny nose, stuffy nose, shortness of breath, or wheezing) compared to 43% ATA, 30% CRS, 43% NP, and only 14% in healthy controls. This high prevalence did not seem to be related to the severity of the underlying asthma, as it was similar in the patients with ATA and AERD. These reactions occur within minutes of drinking alcohol and do not appear to involve inhibition of COX-1. Interestingly, patients also report a tolerance to alcohol after desensitization and continued therapy with ASA [9]. Studies are ongoing to better understand what is going on in these alcohol-induced respiratory reactions.

Another reason why we may be missing these patients is that we make the assumption that because they are on low-dose aspirin, i.e., 81 mg a day, they must not have AERD. A recent publication identified a group of patients who despite tolerating 81 mg/day of aspirin had positive aspirin challenges when the low-dose aspirin was withdrawn [10]. It is possible that they may have started the aspirin prior to the onset of their disease or did not recognize respiratory reactions induced by the aspirin when they initiated therapy and self-desensitized. For patients with aggressive eosinophilic polyposis, it is worth withholding ASA and doing an oral aspirin challenge to determine if AERD is present, as high-dose ASA therapy is much more effective [11].

Pathophysiology of AERD

Highlights of the recent discoveries will be summarized in this section. Briefly as background, it has been known for some time that AERD is an acquired chronic eosinophilic inflammatory condition of the airways characterized by a type 2 inflammatory response with dysregulation of arachidonic acid metabolism. Key players are mast cells and basophils, eosinophils, T helper 2 cells (TH2), and type 2 innate lymphoid cells (ILC2). There is increased expression of 5-lipooxygenase (5-LO) and LTC4 synthase and upregulation of cysteinyl leukotriene receptors leading to constitutively higher levels of cysteinyl leukotrienes in AERD patients along with hyperresponsiveness to their effects [12–15]. Even in the absence of COX-1 inhibition, the inflammatory process continues due in part to low lipoxin generation, low prostaglandin E2, and one of its target receptors EP 2, which are critical in inhibiting activation of mast cells and eosinophils [16, 17]. With the ingestion of a COX-1-inhibiting NSAID, PGE2 production ceases resulting in the activation of both mast cells and eosinophils with a dramatic release of cysteinyl leukotrienes as well as mast cell and eosinophilic products leading to the characteristic symptoms of bronchoconstriction, rhinitis, conjunctivitis, laryngospasm, and in some cases, hypotension, urticaria, and severe gastrointestinal symptoms (Fig. 1). Although PGE2 is predominantly a COX-2 pathway product, in AERD, there is a relative deficit of COX-2 so that the primary source is the COX-1 pathway [18]. As such, AERD patients can typically take the highly selective COX-2 inhibitors without eliciting a respiratory reaction [19]. Table 1 outlines the key abnormalities known in AERD.

Mixed T_H1/T_H2 Immune Response Given the profound eosinophilic infiltrates in the airways of subjects with AERD, it is not surprising that there are characteristics of TH2-type inflammation with increased IL-4 levels. Steinke et al. have shown increased expression of IFN-gamma mRNA transcripts in nasal polyps from patients with AERD, as compared with aspirin-tolerant and control subjects. This was seen in conjunction with high levels of IL-4 but not IL-5 or IL-13. Both IL-4 and IFN gamma increase LTC4 synthase expression on mast cells and eosinophils [20]. This suggests that AERD is a mixed TH-1/TH2 immune response disease. Their earlier work has shown that IL-4 can inhibit expression of COX-2 and mPGES-1 providing a fuller explanation of the findings in AERD.

Adding to the complexity of the picture is work from Laidlaw et al. that has shown a critical role for platelets in AERD. They found significantly elevated levels of platelet-adherent neutrophils, monocytes, and eosinophils in the blood and sinonasal tissues of patients with AERD [21••, 22]. Platelets express LTC4 synthase and by adhering to granulocytes that express 5-lipooxygenase, they produced

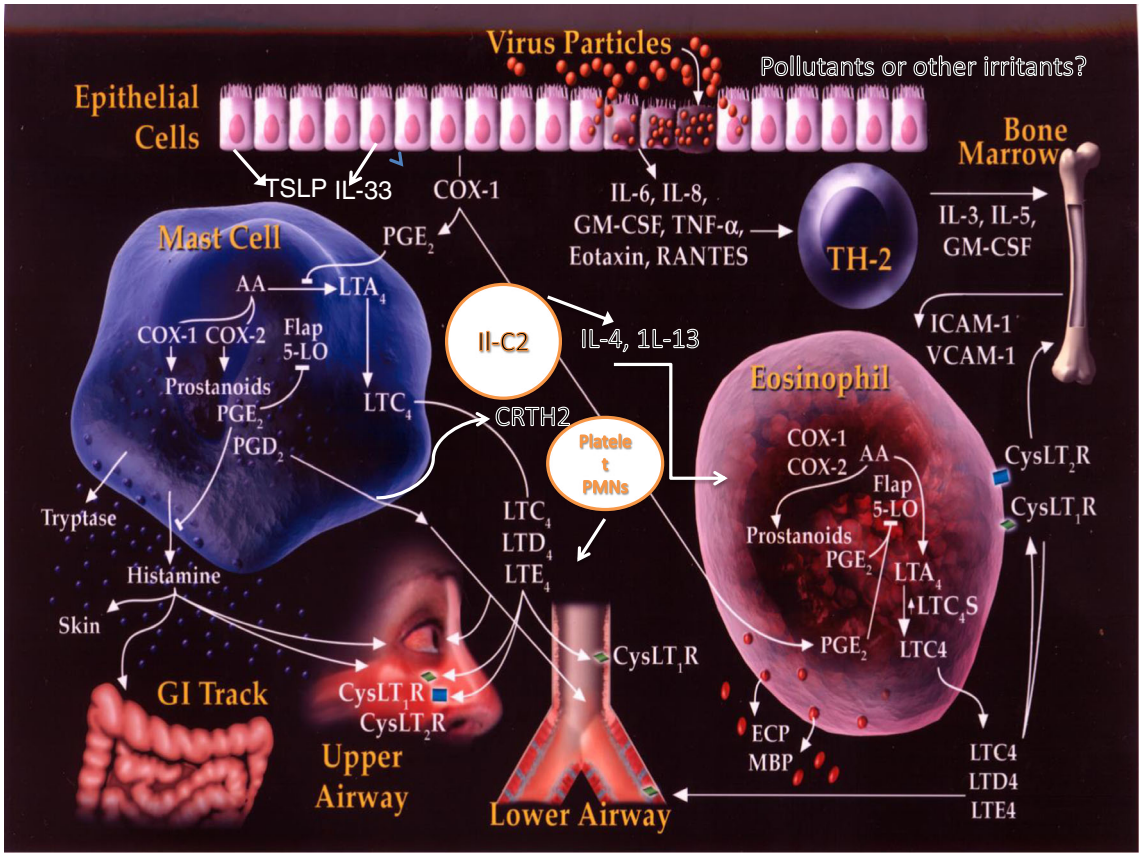

Fig. 1 Updated pathophysiology of AERD. In the absence of exposure to aspirin, there is tremendous ongoing airway inflammation with high levels of eosinophils, mast cells, innate lymphoid type 2 cells (ILC2), T helper 2 cells (TH2), and granulocytes with adherent platelets. The initiating event is unclear but likely involves a viral respiratory illness or other environmental triggers, which damages the epithelium and initiates an innate immune response with the release of thymic stromal lymphopoeitin (TSLP) and interleukin-33 (IL-33) and which in turn activates ILCs, mast cells, and eosinophils. Dysregulation of the arachidonic acid pathway results in very high levels of cysteinyl leukotrienes which along with activated mast cell and eosinophil products elicit the characteristic symptoms of AERD in the target organs of the upper and lower airways, gastrointestinal tract, and skin

70% of cysteinyl leukotriene production through transcellular transfer of metabolic intermediates [21••, 22]. Using a mouse model of AERD, the depletion of adherent platelets was found to attenuate cysteinyl leukotriene formation and NSAID-induced changes in lung function [23].

Table 1 Abnormalities in inflammatory pathways in aspirin-exacerbated respiratory disease

Decrease in prostaglandin E2
Decrease in prostaglandin E2 receptor (EP_2 receptor)
Increase baseline prostaglandin D2 (PGD2)
Increase in thromboxane A2 production
Elevated leukotriene E4 (LTE4) in urine, bronchial lavage, and nasal secretions
Increased airways hyper-responsiveness to challenge with LTE4
Diminished capacity to generate lipoxins
Elevated cysteinyl leukotriene receptor 1 levels ($CysLT_1$ R)
Decreased cyclooxygenase 2 (COX-2) mRNA in nasal polyps

Aspirin desensitization and treatment with aspirin has proven effective in management of patients with AERD. Understanding the mechanisms of how such therapy is effective helps understand the pathophysiology. It has been known for some time that there is a marked decrease in cysteinyl leukotriene 1 receptor expression (cyst LT1 R) [24]. Katial et al. have shown that continued aspirin therapy in patients with AERD leads to decreased IL-4 levels [25]. Looking at the T cell IL-4 signaling pathway, they were able to show that potent COX-1 inhibitors (aspirin and indomethacin) inhibited STAT-6 phosphorylation in a dose-dependent manner with the most striking effects in AERD patients as compared to aspirin-tolerant asthmatics and healthy controls [26].

Prostaglandin E2 and Prostaglandin D2 Known abnormalities in AERD include decreased production of prostaglandin E2 as well as one of its receptors involved in the anti-inflammatory effects of PGE2, EP2 receptor. Machado-Carvahlo et al. showed that reduced expression of COX-2 and mPGES-1 in patients with AERD is closely related to

the low expression of the EP2 receptor [27••]. In AERD, there is low COX-2 expression despite the very significant ongoing inflammatory process. Their observations suggest that abnormal regulation of the autocrine loop regulating the COX-pathway, which includes IL-1R1, COX-2, mPGES, EP2, and PGE2, is involved in the reduced production of PGE2 in AERD. They were able to highlight the importance of the EP2 receptor expression by normalizing the expression of COX-2 and mPGES1 with restoration of EP2 receptor function in their model using cultured nasal polyp fibroblasts from patients with AERD [27••, 28, 29].

PGD2 Prostaglandin D2 is a major COX pathway product of mast cells and eosinophils. PGD2 is a potent bronchoconstrictor and vasodilator acting at the T prostanoid (TP) receptor and D prostanoid type 1 (DP1) receptors, respectively. It is the primary ligand for chemoattractant receptor homologue expressed by TH2 cells (CRTH2). PGD2 acts on basophils, eosinophils TH2 cells, and ILC2s to induce chemotaxis. ILC2 cells also express high levels of CRTH2, and stimulation with PGD2 can lead to cytokine generation (IL-4 and IL-13) contributing to the ongoing inflammation characteristic of AERD [30, 31••]. Subjects with AERD have high baseline levels of PGD2 metabolites that increase dramatically with aspirin-induced reactions. Cahill et al. have shown that the rise in PGD2 is correlated with sinonasal symptoms and decline in FEV1 with a concomitant increase in blood eosinophil levels [32]. Although PGD2 is traditionally thought of as a mast cell product, Feng et al. demonstrated that eosinophils can synthesize PGD2 at significant levels. In AERD where there is a massive influx of eosinophils, PGD2 and its receptor CRTH2 are emerging as attractive targets for directed therapy.

There is an emerging understanding of the role of the innate immune response in AERD with particular attention focused on the ILC2 cells. Work from Boyce and Laidlaw laboratories has shown increased levels of IL-33 and TSLP (thymic stromal lymphopoietin) in polyps from AERD subjects [32, 33]. These cytokines can directly drive eosinophilic inflammation, mast cell activation, and IgE synthesis without involvement of the adaptive immune response [34]. A recent review from Cahill and Boyce highlights this rapidly evolving area of research [35••].

Figure 1 highlights the known pathophysiology of AERD. It is a tribute to the dedication of Szczeklik and Stevenson to their decades of work on understanding AERD. The figure builds on what they laid out in 2003 [36•]. What was not known then was the role of ILC2s and platelet-adherent granulocytes. What is still not known is what initiates the disease although it presumed to be an altered innate response to an infectious or other environmental exposure.

Update in the Diagnosis and Management of AERD

Diagnosis of AERD is dependent upon a provocative challenge to aspirin (ASA), lysine-ASA, or other NSAID as there are no validated in vitro tests [37, 38]. Although a history of respiratory reactions with ingestion of NSAIDs is helpful, it is not diagnostic. A history of multiple NSAID-induced reactions, age less than 40, and poor or absent sense of smell were statistically associated with higher likelihood of having a positive oral aspirin challenge (OAC) [39]. In patients referred for OAC who had nasal polyps and asthma but no historical reaction to ASA/NSAIDs, only 42% had a positive challenge. For patients with a history of 1 NSAID-induced respiratory reaction, 80% will have a positive challenge, this goes up to 89% if they had experienced two or more reactions. Finally, 100% will have a positive OAC confirming diagnosis of AERD if the historical reaction was severe. In that same study, 16% of patients who thought they had aspirin-sensitivity had a negative challenge, highlighting the need for confirmatory OAC.

Standard management of AERD includes avoidance of COX-1-inhibiting NSAIDs, guideline-based treatment of asthma, and chronic rhinosinusitis along with use of leukotriene-modifying medications. In many instances, ASA desensitization and treatment with high-dose aspirin is beneficial [40, 41]. A recent survey of 190 patients with AERD disease found that the patients relied upon a number of resources other than their physicians for treatment [42]. When asked specifically about treatment, high-dose aspirin therapy was rated as the most effective treatment but only half the patients who had been offered aspirin desensitization went through with the procedure. The next most effective therapy was zileuton, a 5-lipooxygenase inhibitor, but only 24% of the patients in the study had been given a trial of zileuton. This study highlights the need for better management for these patients and, at the very least, suggests that a trial of zileuton is warranted.

Aspirin Desensitization

If a patient with AERD is requiring multiple sinus surgeries for recurrent polyposis and cannot be managed successfully with topical steroids, long-acting beta-agonists, and leukotriene-modifying drugs, they should be considered as candidates for aspirin desensitization and treatment with high-dose ASA [43]. Additionally, patients requiring ASA or NSAID therapy for other conditions such as cardiovascular disease or rheumatologic conditions are also ideal candidates [44]. Aspirin challenge and desensitization procedures can be safely done in the outpatient setting with trained staff and physicians. For patients with severe rhinosinusitis/polyps, it is recommended that the desensitization be carried out 2–4 weeks after surgical debulking.

Although multiple protocols for aspirin challenge and desensitization have been published, there are some key factors to keep in mind when choosing which protocol to use. Firstly, the historical reaction does not predict the outcome of aspirin challenge so the patient who had respiratory arrest due to full-dose aspirin (650 mg ASA) may safely undergo outpatient aspirin challenge and desensitization [45]. Second, the average time to onset of symptoms after the provoking dose of aspirin is 102 min with the typical provoking dose being between 45 and 100 mg of ASA [46]. Therefore, protocols with accelerated dosing schedules should be viewed with caution. It should be recognized that the OAC and desensitization process includes confirming diagnosis of AERD with a positive respiratory reaction. Once that has occurred, the additional dosing of aspirin results in desensitization. Table 2 provides a succinct summary of the protocol we are currently using. It typically takes 1.5 days.

Acute desensitization is associated with an improvement in nasal congestion. This one factor makes doing a double-blind placebo-controlled trial very challenging. There is a refractory period of 2–5 days after which patients return to their baseline sensitivity. Aspirin desensitization results in cross-desensitization to all COX-1-inhibiting NSAIDs. In analysis of safety of over 1400 patients who underwent desensitization to ASA, only three (0.002%) experienced systemic reactions and all responded to one dose of epinephrine [47••].

Table 2 Nasal ketorolac and oral aspirin challenge protocol

Time	Dose
Day 1	
8:00 AM	1 spray ketorolac (1 spray in one nostril)
8:30 AM	2 sprays ketorolac (1 each nostril)
9:00 AM	4 sprays ketorolac (2 each nostril)
9:30 AM	6 sprays ketorolac (3 each nostril)
10:30 AM	60 mg aspirin
12:00 PM	
3:00 PM	60 mg aspirin
	DISCHARGE PATIENT
Day 2	
8:00 AM	150mg aspirin
11:00 AM	325 mg aspirin[a]
2:00 PM	DISCHARGE PATIENT

Preparing nasal ketorolac:
1. Take ketorolac (60mg/2mL) and mix with preservative-free normal saline (2.75 mL).

2. Place combined solution in a nasal spray bottle (one that delivers 100 microliters/actuation).

3. Prime with 5 sprays before use. Each spray will now actuate 1.26 mg of ketorolac solution.

4. Patient should tilt head down during sprays and sniff gently to avoid swallowing solution.

1. Spirometry (FEV1) and objective clinical evaluation should be performed prior to each dose

2. Treat reactions appropriately and wait until symptoms resolve

a. Reactions are classified as follows:

i. Naso-ocular

ii. Naso-ocular with ≥15% decline in FEV1 (“Classic reaction”)

iii. Lower respiratory reaction (≥20% decline in FEV1)

iv. Laryngospasm with or without i., ii., or iii.)

v. Systemic reaction (urticaria, gastrointestinal symptoms, hypotension)

3. Aspirin desensitization:

a. After reactions are treated and resolve, continue next scheduled ketorolac dose OR repeat oral provoking aspirin dose

b. Desensitization is complete after 325 mg of aspirin

c. Patient should take 650 mg of aspirin that evening then continue 650 mg twice daily as their continuous aspirin dose until further instructed

[a] If no reaction occurs within 3 h after 325 mg dose, consider it a negative challenge

Aspirin desensitization and treatment with high-dose aspirin has been shown to be a cost-effective intervention in patients with moderate to severe AERD [48]. Studies dating back to the early 1980s have confirmed the benefit of aspirin therapy in AERD [2]. More recent placebo-controlled studies have confirmed the benefit of aspirin therapy with reduction in sinonasal and asthma symptoms, use of medications, and improvement quality of life [11, 49]. Aspirin desensitization and high-dose aspirin therapy have been shown to slow polyp regrowth thereby reducing need for repeated sinus surgeries, improve sense of smell, and reduce frequency of sinus infections [3•, 50, 51]. These benefits can be seen as early as 4 weeks post-desensitization [52].

Recently, there has been a subset of AERD patients identified in which aspirin desensitization and therapy are particularly challenging. They are characterized by having dramatically high levels of PGD2 during their aspirin-induced reactions along with severe gastrointestinal and cutaneous symptoms despite pretreatment with leukotriene-modifying drugs and antihistamines [29]. It has been suggested that these patients may not undergo successful aspirin desensitization with failure to desensitize. It has been our experience that in addition to montelukast, zileuton, and high-dose cetirizine, addition of misoprostol, a synthetic PGE2 analog with or without oral cromolyn, will allow for successful desensitization. We recently reviewed our data of 164 consecutive aspirin challenge and desensitizations of which 17 had severe gastrointestinal and cutaneous reactions and we were all successfully desensitized (data in press). Reviewing over 2500 OAC and desensitization procedures at Scripps, only two patients were not able to be successfully desensitized. One of the two patients returned after a Nissen fundoplication for reflux and had a successful desensitization. These patients often require 3–4 days for desensitization and the GI and cutaneous symptoms can be quite severe.

Aspirin Dosing

The desensitized state may be maintained with 81 mg/day of ASA. Unfortunately, that dose is not effective in treating AERD [2]. For patients with well-controlled airways disease who need cardiovascular prophylaxis with ASA, they may remain on the 81 mg a day. Optimal dosing seems to be between 325 and 650 mg ASA BID. A study comparing aspirin 325 mg BID versus 650 mg twice a day found that about half of the patients did well on the lower dose whereas half required the higher dosing with a lower incidence of dyspepsia seen in the high-dose ASA group [53]. As it was not possible to predict who would do well at which dose, it is recommended to start at the high dose, ASA 650 mg twice a day for 2 months, and assess response. If doing well, you can drop the dose down to 325 mg twice a day. If there is a gradual increase in nasal congestion, loss of sense of smell, or need for more medications, go back to the higher dose of aspirin.

Silent Desensitization

A potential pitfall in the management of AERD was highlighted in a case report of seven patients with suspected AERD who underwent aspirin challenge and desensitization but had no symptoms during the procedure. Given the very strong clinical history, the decision was made to re-challenge these patients off of montelukast with the outcome being a positive challenge [9]. Fortunately, this appears to be a very rare phenomenon. If there is a high suspicion for AERD in the face of a negative OAC, the options would be to stop the leukotriene modifier and repeat the challenge or assume that the patient truly has AERD and treat for 6 months with high-dose aspirin and reassess response at that time point [9].

Absolute contraindications to aspirin desensitization include a history of gastric ulcers, unstable asthma, significant renal or liver disease, and planned pregnancy. If a patient who has undergone aspirin desensitization and forgets to take their aspirin, the following guideline can be helpful: if less than 3 days since last dose of ASA, they can restart at full dose at home. If it is between 3–5 days since last dose, restart ASA at 81 mg and at 90-min intervals, double the dose until 325-mg dose reached and then resume previous dosing of ASA. This can be done in the office. If it has been greater than 5 days, re-challenge starting at the patient's previous provoking dose. Table 3 shows the guidelines for dosing aspirin for anticipated surgeries. For procedures such as colonoscopies even with planned polypectomy, there is no need to discontinue aspirin. Working with our head and neck surgeons, we typically maintain aspirin even through sinus surgery. For the surgeon that requires the patient to stop aspirin, we have a protocol in Table 3 that prevents the need for repeat aspirin desensitization.

Table 3 Protocol for continuation of aspirin during elective surgery

1. Decrease aspirin dose to 325 mg each day, beginning 8 days before surgery.
2. Two days before surgery, take your last aspirin tablet in the morning.
3. On the day before the surgery and the morning of the surgery, DO NOT TAKE ANY ASPIRIN
4. After completing the operation and when you are completely recovered from anesthesia, take one aspirin 325-mg tablet.
5. On the day after surgery (post-op day 1), take one 325-mg tablet of aspirin in the morning and one 325-mg aspirin at night.
6. On the second day after surgery (post-op day 2), take your usual dose of aspirin (i.e., whatever dose you were doing prior to the surgery).

Other Therapies for AERD

Omalizumab has been identified as a possible therapy for AERD with several case reports suggesting efficacy [54, 55]. A more recent double-blind placebo-controlled trial of omalizumab in patients with nasal polyps and asthma found a significant decrease in the total nasal endoscopic score in the treatment arm of which 12 of the 24 patients had a history of aspirin sensitivity, which had not been confirmed by challenge making extrapolation to AERD patients difficult [56]. A recent report from Japan looked at 21 adults with challenge-proven AERD and documented aeroallergen sensitivity treated with omalizumab. Fifty-two percent of the patients had a rapid response within the first week of treatment. They were also able to show a significant reduction in both urinary LTE4 and PGD2 metabolites [57]. Review of recent patients undergoing OAC and desensitization is presented at Scripps. We reviewed all patients undergoing OAC and desensization at Scrippps Clinic looking specifically at impact of omalizumab on outcomes. Eight patients who were on omalizumab had a positive OAC whereas there was only 1 subject on omalizumab of the 37 patients who had a negative challenge suggesting that omalizumab does not block aspirin reactions in patients with AERD. There needs to be further studies in AERD to elucidate both the mechanism of action and role in treatment before it can be recommended.

Diet There have been links reported between dietary salicylates and AERD [58]. Salicylates do not inhibit the COX-1 enzyme and therefore the role in the pathology of AERD remains unclear. Building upon an earlier pilot study of a low-salicylate diet in patients with AERD, Sommner et al. performed a multicenter randomized crossover trial in patients with presumed AERD (history of NSAID reactions and sinus disease, but not challenge-proven) and were randomized to either a low-salicylate diet for 6 weeks or a regular diet and then after a washout, crossed over to the other diet [59]. Treating physician was blinded to the diet but patients were not blinded, as they had to follow a low-salicylate diet. They were able to show a significant improvement in SNOT 20 scores but the study had limitations that it was not adequately powered, as they were not able to enroll the prerequisite number of patients. The diet itself is difficult as sources of salicylates include fruits, many vegetables, spices, herbs, almonds, and certain oils making long-term adherence challenging. It is not our recommendation to consider dietary manipulation for treatment of AERD.

Conclusions

AERD is a complicated inflammatory disease associated with profound dysregulation of eicosanoid metabolism, activated effector cells including eosinophils, mast cells, T cells, ILC-2s, platelets, and respiratory epithelial cells. As the understanding of the pathophysiology grows, the potential for targeted therapy will help improve clinical outcomes. A mainstay of therapy for moderate to severe AERD remains aspirin desensitization and high-dose aspirin therapy. It remains to be seen what role the biologic agents such as omalizumab, anti-platelet therapy, anti-IL-5 therapies, and dupilamab will have in the management of AERD. It is critical to recognize these patients early in the disease course to potentially prevent life-threatening respiratory reactions with inadvertent NSAID/ASA exposure and to improve quality of life. Clinical features such as pan-sinusitis, aggressive nasal polyposis, and sensitivity to alcohol should suggest the possibility of AERD. In addition, for patients followed over time, it is worth reassessing for aspirin sensitivity if those sorts of clinical features begin to present.

Compliance with Ethical Standards

Conflict of Interest Dr. Woessner declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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