

Aspirin-Exacerbated Diseases: Advances in Asthma with Nasal Polyposis, Urticaria, Angioedema, and Anaphylaxis

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Abstract Aspirin-exacerbated diseases are important examples of drug hypersensitivities and include aspirin-exacerbated respiratory disease (AERD), aspirin- or non-steroidal anti-inflammatory drug (NSAID)-induced urticaria/angioedema, and aspirin- or NSAID-induced anaphylaxis. While each disease subtype may be distinguished by unique clinical features, the underlying mechanisms that contribute to these phenotypes are not fully understood. However, the inhibition of the cyclooxygenase-1 enzyme is thought to play a significant role. Additionally, eosinophils, mast cells, and their products, prostaglandins and leukotrienes, have been identified in the pathogenesis of AERD. Current diagnostic and treatment strategies for aspirin-exacerbated diseases remain limited, and continued research focusing on each of the unique hypersensitivity reactions to aspirin is essential. This will not only advance the understanding of these disease processes, but also lead to the subsequent development of novel therapeutics that patients who suffer from aspirin-induced reactions desperately need.

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Introduction

The spectrum of aspirin-exacerbated diseases is broad, encompassing single organ involvement to systemic anaphylaxis, and has great impact on those patients who suffer from these diseases. The ease of access to aspirin worldwide, the medicinal value of aspirin for both cardiovascular and inflammatory conditions, and the frequency with which these diseases occur make a current understanding of aspirin-exacerbated diseases essential for any medical provider evaluating and treating adverse drug reactions. This update will review the cutting-edge knowledge about aspirin-exacerbated respiratory disease (AERD), aspirin-induced urticaria/angioedema, and aspirin-induced anaphylaxis.

AERD: Clinical Advances in Diagnosis and Management

Novel Insights into the Clinical Characteristics of AERD

AERD is one of the most recognized conditions associated with worsening symptoms following the ingestion of aspirin. This disease has long been defined by the presence of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and a hypersensitivity to all medications that inhibit the cyclooxygenase (COX)-1 enzyme. Within minutes to hours of ingesting medications such as aspirin or ibuprofen, patients with AERD can develop a variety of symptoms, with respiratory symptoms such as rhinorrhea, nasal congestion, cough,

wheeze, and dyspnea being the most common. Gastrointestinal symptoms including sharp abdominal pain, nausea, and/or diarrhea have also been reported, albeit less frequently than respiratory symptoms. More recently, a study by Cahill and colleagues identified a subset of patients with AERD who, after ingesting aspirin, developed a pruritic and erythematous skin rash on their distal upper and lower extremities, often in association with gastrointestinal symptoms, clinically distinct from that classically observed in aspirin-induced urticaria [1••].

There is heterogeneity among the population of patients diagnosed with AERD because symptom severity can vary greatly among affected patients. In an attempt to better characterize AERD disease heterogeneity, Bochenek and colleagues performed a latent class analysis to identify subphenotypes of AERD using data from over 200 AERD patient surveys and clinical laboratory results [2]. From their analysis, they identified four subsets of AERD patients based upon specific asthma characteristics: (1) moderate asthma associated with peripheral eosinophilia, (2) mild asthma that is relatively well controlled with low health care utilization, (3) severe asthma that is poorly controlled with evidence of pulmonary obstruction, and (4) severe asthma that is poorly controlled and only observed among females. It is important to note, however, that only ~81 % of the participants in this study who had asthma and aspirin intolerance were also diagnosed with nasal polyps. It remains unclear whether the ~20 % of patients who did not have nasal polyps are distinct from the ~80 % with the triad of asthma, CRSwNP, and COX-1 inhibitor hypersensitivity, and further studies are needed to address this.

While most patients with AERD report reactions to all COX-1 inhibitors, patients with CRSwNP and asthma who take a daily low-dose aspirin should not automatically be discounted as having AERD [3]. Lee-Sarwar and colleagues identified 7 of 163 patients in their cohort who tolerated 81 mg of aspirin daily just prior to a formal positive aspirin challenge. The mechanism of tolerance of low-dose aspirin is unknown but may be due to the dose being below the threshold for clinical reaction [4, 5].

Even in the absence of aspirin ingestion, patients with AERD have distinct clinical features that help to distinguish them from patients with asthma or CRSwNP alone. In a survey of 59 patients with AERD at two academic institutions, over 80 % reported developing nasal congestion, rhinorrhea, shortness of breath, and/or wheezing following ingestion of alcohol [6•]. These reactions occurred at a higher frequency than in aspirin-tolerant (AT) patients with either asthma (43 %) or chronic sinus disease (43 %). Interestingly, the respiratory reactions within the AERD cohort occurred within minutes to hours regardless of the type or amount of alcohol consumed and can be improved with aspirin therapy [6•, 7].

Studies have also shown that AERD patients report a decreased quality of life despite avoidance of COX-1 inhibitors [8, 9]. Additionally, these patients often have more significant

sinonasal inflammatory disease and undergo more sinus surgeries as part of disease management when compared to AT patients with CRSwNP [9, 10]. Likewise, AERD patients typically have more severe asthma, as shown by reduced pulmonary function and greater requirement for high-dose corticosteroid therapies, when compared to AT asthmatics (ATA) [11]. Patients with AERD were significantly more likely to have severe asthma with an 80 % increase in emergency room visits and a 40 % increase in asthma hospitalizations when compared to ATA [12]. Likewise, increased numbers of prior emergency department visits and hospitalizations, as well as having elevated IgE levels, were associated with significantly worse asthma control among AERD patients [13]. Factors significantly associated with improved asthma control in AERD included receiving medical care in a specialty referral clinic and undergoing nasal polypectomies to manage sinus disease [13].

Advances in Diagnosis and Treatment of AERD

Clinical risk factors significantly associated with having AERD include age less than 40 years, poor sense of smell, and history of multiple prior respiratory reactions to aspirin (and non-steroidal anti-inflammatory drugs (NSAIDs)) [14]. While obtaining a thorough medical history is critical when evaluating patients for possible AERD, it has been estimated that as many as 15 % of patients with a convincing clinical history of asthma, CRSwNP, and hypersensitivity to a COX-1 inhibitor do not, in fact, have the disease [15]. Although the clinical experience of the authors suggests a 15 % negative aspirin challenge rate is high, there have been no known published studies to challenge this number. As such, the gold standard for diagnosing AERD remains an aspirin challenge, since no in vitro diagnostic tests have been validated to date [16, 17]. Classically, a positive challenge (or confirmation of the diagnosis of AERD) occurs when an upper and/or lower respiratory tract reaction occurs during the challenge procedure.

Previously, it was thought that a patient who remained asymptomatic throughout the entire aspirin challenge did not have AERD. However, a recent study by White and colleagues has identified a cohort of patients with an initially negative aspirin challenge who developed a positive reaction on secondary re-challenge [18]. These patients were classified as having a “silent challenge/desensitization” and considered to have AERD. Why certain patients can be silently challenged and what mechanisms contribute to this observed phenomenon remain unclear, but pre-treatment with medications such as leukotriene antagonists may play a role in this unique cohort [19].

Unfortunately, treatment options for patients with AERD remain somewhat limited. Sinonasal disease and asthma can be medically managed with standard glucocorticoid and

leukotriene modifier therapies [20, 21]. Omalizumab, a humanized monoclonal antibody that binds to IgE, is effective for treating asthma and has shown promise in clinical studies of CRSwNP [22, 23]. Clinical trials of omalizumab in AERD are underway with results expected in late 2015. Finally, a small clinical trial in CRSwNP reported that mepolizumab, a humanized monoclonal antibody that inhibits IL-5, was associated with an improvement in nasal polyps compared to placebo [24]. In this study, 25 % of participants had AERD suggesting that mepolizumab could be another treatment option in AERD but further clinical investigations are warranted.

Aspirin desensitization followed by continued daily aspirin ingestion is known to improve patient quality of life, reduce symptoms, and slow the regrowth of nasal polyps in as many as 70–80 % of patients with AERD [4, 25–28]. Furthermore, this therapy can augment the clinical improvements observed following sinus surgery alone. A recent case-control study found that after 1 year, aspirin-desensitized patients who underwent desensitization after sinus surgery had significant improvement in nasal symptoms, sense of smell, and nasal polyps with no change in severity of patient-reported asthma symptoms when compared to AERD patients who were not desensitized [29]. In another small study, improvements in nasal polyp scores following sinus surgery in patients with AERD were preserved for at least 30 months by aspirin desensitization [30]. These studies support that aspirin desensitization can result in significant long-term improvements in quality of life as well as a reduction in the need for medical therapies and remains the treatment of choice for refractory cases requiring frequent prednisone and/or surgical intervention.

While 650–1300 mg of aspirin per day is the traditionally recommended daily maintenance dose following desensitization [31], 300 mg of aspirin daily has also been shown to be effective [32]. Evidence for even lower doses of aspirin, such as 100 mg daily, is conflicting [33, 34]. Oral preparations or nasal lysine aspirin, which is not currently available in the USA, are equally beneficial for treating AERD [35].

Surgical intervention is another common therapeutic option available for managing patients with AERD. A recent meta-analysis reviewed over 300 studies between 1946 and 2014 to examine the effects of sinus surgery in AERD [9]. Studies of adult patients who underwent any form of sinus surgery as a primary intervention for AERD, who were followed for at least 3 months post-operatively and who received no concomitant additional therapies, were included. From the 16 studies that fulfilled inclusion criteria, endoscopic sinus surgery significantly improved patient quality of life as well as sinonasal inflammation measured by sinus CT and nasal endoscopy [9].

Diet modifications have also been proposed to be effective. A recent single blind crossover pilot study of ten AERD patients demonstrated significant improvement in patient-reported nasal symptoms, as well as sinonasal inflammation

by CT scan and nasal endoscopy, when eating a low salicylate versus a regular diet [36]. However, interpretation of these results is limited by small sample size, lack of aspirin challenges to confirm the clinical history of AERD, and absence of a wash-out period between the study arms. These findings highlight the need for larger and more comprehensive studies evaluating if diet could contribute to AERD pathogenesis.

Overall, current treatment options are suboptimal for many AERD patients, and additional studies are warranted to identify and develop new pharmacologic strategies for the medical management of AERD. Novel therapeutics for AERD are entering phase II and III clinical trials, and the authors anticipate expanded treatment options in the near future.

AERD: Advances in Our Understanding of Mechanism

Dating back to the early work of Andrew Szczeklik in 1975, the respiratory reactions elicited by aspirin and other NSAIDs in AERD are known to be the result of COX inhibition [37]. Subsequent work highlighted the impaired prostaglandin (PG)_{E2} production, the overproduction of cysteinyl leukotrienes (cysLT), and the mast cell activation that contribute to the aspirin-induced respiratory reactions in AERD [38–40]. All of these remain the central tenants of our understanding of AERD pathophysiology at present (Fig. 1). In recent advances, PGD₂ has emerged as a central mediator of AERD, and the roles of effector cells, eosinophils and mast cells, and cytokines are better understood.

Prostaglandin D₂

Prostaglandin D₂ is known to signal through three receptors, DP1, CRTH2, and TP, to mediate vasodilation, effector cell chemotaxis, and bronchoconstriction, respectively. In a cohort of subjects with AERD who underwent aspirin challenge/desensitization followed by high-dose aspirin therapy, Cahill and colleagues identified a key role for PGD₂, particularly in those individuals who develop cutaneous and gastrointestinal symptoms during aspirin challenge [1•]. In AERD, PGD₂ is elevated at baseline in comparison to ATA controls and, following a single 325-mg dose aspirin challenge, PGD₂ levels increased in AERD patients while they decreased in ATA [1•, 41, 42]. Following desensitization and 8 weeks of 1300 mg of aspirin daily, PGD₂ was dramatically suppressed, cysLTs remained unchanged, and peripheral blood eosinophils were elevated compared to pre-desensitization baselines in AERD subjects [1•]. These findings support the hypothesis that PGD₂ contributes to disease symptoms at baseline, as well as during an aspirin challenge, and it plays a role in effector cell recruitment in AERD. Furthermore, the reduction of PGD₂ with daily aspirin therapy is a potential explanation

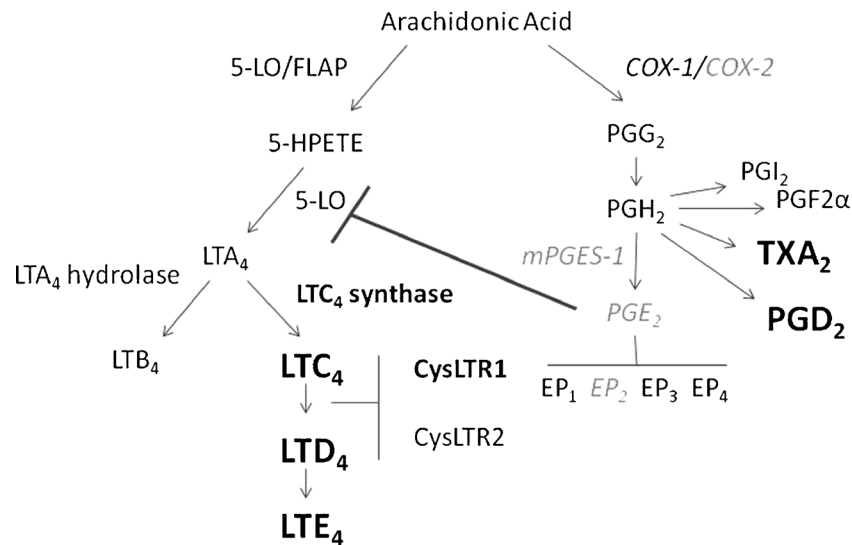


Fig. 1 Mediators, receptors, and enzymes implicated in impaired arachidonic acid metabolism in the pathogenesis of aspirin-exacerbated respiratory disease. Multiple steps involved in the generation of arachidonic acid have been implicated as dysfunctional in AERD. Those products known to be over-produced including the cysteinyl leukotrienes (LTC_4 , LTD_4 , and LTE_4) and prostaglandin D_2 are in **bold**. In contrast,

those with decreased expression including COX-2, microsomal prostaglandin E synthase (mPGES)-1, prostaglandin E_2 , and the PGE_2 receptor EP_2 are *gray and italicized*. PGE_2 is a known negative regulator of 5-lipoxygenase (LO) activity. Therefore, the decreased amounts of PGE_2 in AERD result in increased generation of the cysLTs

for how aspirin offers a therapeutic benefit in desensitized AERD patients. To this end, the use of novel therapeutics which target PGD_2 signaling in AERD should be further explored.

Eosinophils and Mast Cells

AERD is characterized by the presence of eosinophilic inflammation within nasal polyps and is often associated with peripheral blood eosinophilia. Similarly, the abundant production of PGD_2 and cysLTs at baseline and during aspirin-induced reactions support the role of the mast cell in AERD. It is not known if the eosinophil, an abundant effector cell in AERD, or the mast cell responds abnormally to aspirin and thereby contributes to the respiratory reactions observed in AERD. Two recent publications sought to address these questions. Using a lysine-aspirin nasal challenge, subjects with AERD demonstrated a release of eosinophilic cationic protein and cysLTs in nasal lavage fluid after challenge while no change was noted in ATA subjects [43]. In vitro, peripheral blood eosinophils have been shown to release eosinophil-derived neurotoxin (EDN) following stimulation with lysine aspirin but not other NSAIDs in both AERD and ATA subjects [44]. Additionally, CD34+ progenitor-derived mast cells demonstrated PGD_2 production in response to lysine aspirin stimulation [44]. Together this work suggests aspirin may directly activate eosinophils and mast cells, but additional studies are needed to completely define the role eosinophils and mast cells play in the pathogenesis of AERD.

Platelets

In addition to the classical cells of the innate immune system, recent work has identified a specific role for platelets in AERD. Laidlaw and colleagues reported increased platelet-granulocyte aggregates in the peripheral blood of subjects with AERD compared with ATA as well as their identification of platelets which co-localized with leukocytes in the nasal polyp tissue [45••]. In subjects with AERD, the percentage of platelet-granulocyte aggregates correlated with systemic cysLT production. Additionally, they provided strong evidence to suggest that adherent platelets increase cysLT generation from granulocytes by contributing LTC_4S activity, thereby playing a major role in cysLT production in AERD. This increase in platelet-eosinophil aggregates and the correlation with cysLT production was recently corroborated in a second, ethnically unique, AERD population [46]. These data served as the foundation for an ongoing clinical trial investigating the therapeutic role for anti-platelet agents in AERD with results expected in 2016. A recent review highlights the mouse and human studies which identify a role for platelets in the pathophysiology of AERD [47•].

Cytokines and Other Inflammatory Mediators

AERD nasal polyp tissue is characterized by a prominent type-2 inflammatory environment with studies showing elevated levels of interleukin (IL)-5, IL-13, eotaxin-1, eotaxin-2, and eosinophil cationic protein (ECP), an eosinophil granule protein, when compared to healthy sinonasal tissue [48, 49, 50••].

Additional studies have provided conflicting results regarding levels of various inflammatory mediators in nasal polyps of patients with AERD compared to polyps from patients with CRSwNP. Stevens and colleagues recently reported significantly elevated levels of ECP, granulocyte macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein (MCP)-1 in AERD compared to polyps from patients with CRSwNP, but no differences in other mediators including IL-5, IL-13, eotaxin-1, eotaxin-2, or interferon (IFN)- γ were found [50••]. This is in contrast to other studies that found elevated levels of IL-5 or IFN- γ in AERD versus CRSwNP nasal polyps [48, 49, 50••]. Such discrepancies could possibly be explained by differences in corticosteroid use within the study populations or the type of assay used to measure inflammatory mediator levels in nasal polyp tissue.

In the peripheral blood, Aktas and colleagues demonstrated a baseline reduction in IFN- γ -secreting CD4+ T lymphocytes in AERD compared with healthy controls but no change in the percentage of CD4+ T lymphocytes expressing IFN- γ , IL-2, or IL-4 prior to and following aspirin desensitization [51]. In a follow-up study in a larger cohort, the same group reported a higher frequency of CD4+ T cells expressing IL-10 or IFN- γ in AERD compared to controls. Moreover, aspirin desensitization followed by daily aspirin therapy in AERD patients induced a decrease in frequency of CD4+ T cells expressing IL-10 or IFN- γ to a level that was similar to that seen in controls [52]. Taken together, additional research is necessary to fully characterize the cytokine profile unique to AERD and to determine the contribution of cytokines to this disease.

IgE

The reactions observed in AERD following aspirin ingestion are not considered secondary to an IgE-mediated hypersensitivity response toward aspirin. However, atopy is common among patients with AERD, and elevated levels of total IgE within nasal polyp tissue from CRSwNP have been identified [15, 53, 54]. Elevations in total serum IgE have been reported in non-atopic AERD patients as well as in those with positive skin testing [55, 56]. Specific IgEs to staphylococcal superantigens have been associated with increased methacholine hyperresponsiveness, higher eosinophil counts, and higher total serum IgE [56] although there are conflicting reports as to whether these specific antibodies are elevated in AERD versus AT nasal polyps [56–58]. The contribution of IgE to baseline and aspirin-induced symptoms as well as the potential benefit of IgE target therapies requires additional investigation.

Genetics of AERD

AERD classically develops in adulthood and is not associated with an underlying Mendelian pattern of inheritance.

However, numerous studies have been published on potential genetic variants that could be responsible for why certain patients develop AERD [59–62]. Additional investigations are needed to validate these initial findings and currently no confirmed genetic abnormality exists in AERD.

Epidemiology of AERD

The financial burden of managing AERD can be substantial. In 2014, the cost of medical care 1 year prior to sinus surgery was estimated to be over \$2000 per patient per year for those with AERD as compared to \$300 per patient per year for those with no respiratory comorbidities [63]. Additionally, in 2014 US dollars, the average cost of functional endoscopic sinus surgery and post-procedure follow-up currently ranges between \$8200 and \$10,500 [64]. AERD patients on average require more revision sinus surgeries than patients with CRSwNP alone which further increases the overall cost of this disease. In addition to the financial cost of managing AERD, the emotional cost of this disease is also significant. In a recent survey of 190 patients with AERD, the majority reported frustration living with their condition [8]. To this end, 87 or 89 % of surveyed AERD patients reported that chronic nasal symptoms, or a decreased sense of smell, negatively impacted their quality of life, respectively [8].

Despite the significant comorbidity and the large socioeconomic burden associated with AERD, the true number of patients affected by this disease remains unclear. The recent study by Rajan and colleagues offers one of the most comprehensive analyses of AERD prevalence to date [65••]. This large meta-analysis reviewed over 1500 published studies and identified 27 that fulfilled their inclusion criteria. From this, AERD was noted in as many as 12.4 % of asthmatics with an even higher prevalence among severe asthmatics (~15 %). Additionally, 9.7 % of patients with nasal polyps, and 8.7 % with chronic rhinosinusitis, were found to have AERD. As not all patients in these studies underwent confirmatory aspirin challenges, it is possible the prevalence of AERD within certain populations was over- or even underestimated. However, given the size of the analysis, these results are probably some of the best estimates currently available.

Asthma is more prevalent in women and female sex can be associated with more severe disease [66, 67]. Among patients with CRSwNP, there is recent evidence to suggest women have more severe disease and are more likely to have AERD than men [68]. Together, these studies highlight sex differences may influence the development of AERD. Much more is needed to confirm and expand on these findings.

In summary, several recent studies have been published that have helped to advance the clinical understanding, diagnosis, and management of patients with AERD. However, numerous unanswered questions still remain and novel

beneficial therapeutic options have yet to be discovered. These unmet needs can hopefully be addressed through basic scientific research focused on characterizing the mechanisms responsible for AERD pathogenesis and translational studies that employ therapeutics focused at novel targets.

Other Forms of Aspirin Hypersensitivity

NSAID-Exacerbated Cutaneous Disease

In addition to AERD, there are several other types of hypersensitivity to aspirin and NSAIDs. Some are related to the COX-1-inhibiting properties of the drug, while others are presumed IgE-mediated reactions. NSAID-exacerbated cutaneous disease (NECD) manifests as exacerbation of urticaria following aspirin or NSAID exposure in a patient with a history of chronic urticaria. NECD was recently found to represent approximately 12 % of chronic urticaria patients [69••]. While NECD patients develop exacerbations of urticaria following aspirin/NSAID exposure, they also experience idiopathic urticaria and develop exacerbations of urticaria in response to other triggers. In a recent study by Sanchez-Borges et al., patients with NECD were found to have longer duration of urticaria, more angioedema, and increased atopy as compared to chronic spontaneous urticaria without NSAID sensitivity [69••]. The underlying pathobiology is thought to be secondary to the increased release of cysLTs by inflammatory cells following COX-1 inhibition [70]. These aspirin-associated urticarial reactions have been shown to be associated with increased urinary excretion of LTE₄ and PGD₂ [71]. Treatment involves avoidance of all NSAIDs and the cadre of therapeutics effective in AT chronic urticaria. Even in the absence of NSAID exposure, patients often still need treatment for underlying chronic urticaria [70].

NSAID-Induced Urticaria/Angioedema

NSAID-induced urticaria/angioedema (NIUA) is different from NECU in that it develops only after exposure to aspirin/NSAIDs in otherwise healthy patients without a history of urticaria. Symptoms of urticaria and angioedema generally appear 1–6 h after ingestion of NSAIDs. Avoidance of aspirin and NSAIDs typically leads to resolution of symptoms [72]. The underlying pathogenesis of NIUA is not fully elucidated, but there are studies supporting that inhibition of COX-1 leads to the clinical manifestations [73, 74]. Both NECD and NIUA tend to occur with exposure to aspirin and NSAIDs that inhibit COX-1.

Immediate Hypersensitivity Reactions

In contrast to AERD and the NSAID-induced urticarial disorders described above, there are also immediate

hypersensitivity reactions to aspirin or a single NSAID, which may be IgE mediated [75]. Drugs most commonly implicated in single NSAID anaphylaxis include NSAIDs of the pyrazolone class, diclofenac, and ibuprofen [75, 76]. Unlike NSAID-induced urticaria/angioedema, there is no cross-reactivity between chemically dissimilar COX-1 inhibitors. Patients with these hypersensitivities are able to tolerate chemically unrelated NSAIDs but have urticaria, angioedema, and/or anaphylaxis to aspirin or a single NSAID [77].

This diagnosis of single NSAID hypersensitivity can be confirmed with an oral challenge to the culprit medication; however, this approach should be avoided in a patient with a history of severe anaphylaxis. Alternatively, patients can undergo observed challenge to a chemically dissimilar NSAID to rule out cross-reactivity and confirm the safety of an alternative agent [77]. Treatment options include strict avoidance of the implicated NSAID, use of alternative chemically unrelated NSAIDs as needed, and aspirin desensitization if needed [78]. There are not any widely accepted protocols for desensitization to NSAIDs other than aspirin.

The different forms of aspirin-exacerbated diseases and the current understanding of mechanism are summarized in Table 1.

Future Diagnostics for Aspirin Hypersensitivity

A strong clinical history may be able to predict a positive aspirin challenge in 80–100 % of patients being evaluated for AERD [14]. While an observed aspirin challenge remains the gold standard for diagnosing aspirin hypersensitivity in both AERD and NSAID-induced cutaneous diseases, it would be ideal to have a less invasive test to be able to safely diagnose aspirin hypersensitivity without exposing patients to the risk of aspirin challenge and the discomfort of the subsequent reaction. There is currently no widely available, validated in vitro laboratory or skin test to diagnose any aspirin-related disease [79]. Both clinicians and patients would greatly benefit from having a reliable diagnostic biomarker for evaluating AERD and other types of aspirin hypersensitivity [80].

Multiple modalities of in vitro testing have been investigated to diagnose non-AERD aspirin hypersensitivity, including skin prick testing, basophil activation testing, analyses of genetic polymorphisms, and autologous serum skin testing. Skin testing for aspirin and NSAID allergy has been investigated [75, 81], and while skin testing shows promise for some isolated hypersensitivity reactions to single NSAIDs, it is not yet recommended as a diagnostic modality for any type of aspirin hypersensitivity [79]. Basophil activation testing has been studied in patients with a variety of aspirin reactions and has shown mixed results [82–85]. Interestingly, the test has only shown sufficient sensitivity and specificity in patients with cutaneous or anaphylactic reactions [82, 85] but not in patients

Table 1 Features of aspirin-exacerbated diseases

Disease	Baseline disease	Reaction symptoms	Proposed mechanism	Medications eliciting reaction
Aspirin-exacerbated respiratory disease	Asthma with nasal polyps	Classically nasal congestion, rhinorrhea, and bronchospasm Less often gastrointestinal pain, nausea, vomiting, diarrhea, and non-urticarial rash	Impaired PGE ₂ production leads to mast cell activation and PGD ₂ and cysLT overproduction	Aspirin and all COX-1-inhibiting NSAIDs
NSAID-exacerbated cutaneous disease	Chronic urticaria with or without angioedema	Exacerbation of chronic urticaria/angioedema	Reactions associated with increased cysLTs and PGD ₂	Aspirin and all COX-1-inhibiting NSAIDs
NSAID-induced urticaria/angioedema	Healthy at baseline	Urticaria and/or angioedema following aspirin/NSAID exposure	Not fully elucidated, studies support COX-1 inhibition leading to clinical manifestations	Aspirin and all COX-1-inhibiting NSAIDs
Immediate hypersensitivity to aspirin or single NSAID	Healthy at baseline	Urticaria, angioedema, and/or anaphylaxis	Presumed IgE mediated	Single NSAID or aspirin (no cross-reactivity between structurally dissimilar NSAIDs)

with AERD or purely respiratory reactions [83, 84]. While basophil activation testing for the diagnosis of aspirin hypersensitivity requires additional investigation, it may prove to be a useful tool in the diagnosis of non-AERD aspirin hypersensitivity. Commercially available basophil activation tests have not yet been validated.

Aspirin Desensitization for Cardiovascular Disease

Aspirin has a key role in both the primary and secondary prevention of cardiovascular disease including coronary, cerebral, and peripheral vascular diseases [86], as well as in the treatment of acute cardiovascular conditions such as acute myocardial infarction, ischemic stroke, and unstable or stable angina [87]. Patients with cardiovascular disease and history of aspirin hypersensitivity often receive second-line antiplatelet agents resulting in increased risk of hematologic complications and increased cost [88, 89]. A recent retrospective electronic medical record analysis found that 1.5 % of patients with coronary artery disease had a listed history of reaction to aspirin. However, 50 % of these reactions were gastrointestinal bleeding or intolerance, and only 21 % represented true aspirin hypersensitivity [90]. In patients with gastrointestinal bleeding, the concomitant use of a proton pump inhibitor reduces the risk of further gastrointestinal bleeding [91] and does not necessarily preclude aspirin use. Clarifying the nature of the aspirin reaction in patients with cardiovascular disease is of utmost importance in determining appropriate management. Following a careful review of the clinical history, many patients with listed aspirin allergy are determined to have adverse drug effects attributable to the chemical properties of

aspirin such as gastritis or tinnitus and not true hypersensitivity.

For patients with true aspirin hypersensitivity requiring aspirin for treatment of cardiovascular disease, there are a number of published aspirin desensitization protocols [92–96], many with success rates of greater than 90 %. Given the often urgent need for aspirin desensitization in this setting, there is limited literature on well-controlled studies of aspirin desensitization in cardiovascular disease. Furthermore, in many patients undergoing aspirin desensitization for emergent cardiovascular indications, there is no prior observed drug challenge to prove the aspirin allergy. Given the lack of controlled studies, it is difficult to know if the aspirin desensitization is inducing drug tolerance or if it is a prolonged drug challenge. White and colleagues discuss an alternative approach to aspirin challenge and desensitization for patients with cardiovascular emergencies that advocates starting with a higher dose of aspirin (40.5 mg) and proceeding at longer intervals (90 min). This approach allows for challenge and desensitization to occur concurrently. If the patient has a particularly severe history of anaphylaxis to aspirin, a lower starting dose of aspirin can be used [97].

A recent retrospective chart review of patients requiring aspirin for cardiovascular indications found that factors associated with failed desensitization included aspirin reaction within the last year and aspirin-induced angioedema [94]. Another recent study of 43 patients with aspirin hypersensitivity undergoing coronary angioplasty showed a 97 % success rate with a novel intravenous aspirin desensitization protocol. The one patient who failed the protocol had a history of chronic idiopathic urticaria and developed an urticarial rash 12 h after the final step of the aspirin desensitization [96]. Given the importance of aspirin in patients with cardiovascular disease

and the success of rapid aspirin desensitization, allergy consultation should be considered to optimize anti-platelet therapy in this patient group. Aspirin desensitization can be tailored to the individual depending on the urgency of aspirin administration and the nature of the aspirin reaction.

Conclusions

The aspirin-exacerbated diseases remain incompletely understood and with few treatment options. There remains no explanation for the evolution of these diseases in often previously healthy individuals during adulthood. Strict avoidance or aspirin desensitization with daily use, options at complete opposite ends of the therapeutic spectrum, remain the mainstay of treatment nearly 100 years after the first reports of successful aspirin desensitization in AERD [98]. Clinical history and observed aspirin challenge remain the gold standard for diagnosis. The recent identification of a subgroup of patients with AERD who have extremely elevated levels of PGD₂ and the ability of aspirin therapy to suppress PGD₂ has shifted the spotlight in AERD from cysLTs to PGs, the mast cells that produce them, and the eosinophils that respond. This finding supports the development and trial of novel inhibitors that target mast cells, eosinophils, and the PGD₂ pathway in AERD and other aspirin-associated diseases. Results from these studies will advance our understanding of aspirin-associated pathobiology and may provide the next breakthroughs in treatment and diagnosis which have been 100 years in the making.

Compliance with Ethical Standards

Conflict of Interest Drs. Stevens, Buchheit, and Cahill declare no conflicts of interest.

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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- Of major importance

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