



Review article

Aspirin exacerbated respiratory disease: Current topics and trends

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ABSTRACT

Aspirin-exacerbated respiratory disease is a chronic and treatment-resistant disease, characterized by the presence of eosinophilic rhinosinusitis, nasal polyposis, bronchial asthma, and nonsteroidal anti-inflammatory drugs hypersensitivity. Alterations in arachidonic acid metabolism may induce an imbalance between pro-inflammatory and anti-inflammatory substances, expressed as an overproduction of cysteinyl leukotrienes and an underproduction of prostaglandin E2. Although eosinophils play a key role, recent studies have shown the importance of other cells and molecules in the development of the disease like mast cells, basophils, lymphocytes, platelets, neutrophils, macrophages, epithelial respiratory cells, IL-33 and thymic stromal lymphopoietin, making each of them promissory diagnostic and treatment targets.

In this review, we summarize the most important clinical aspects of the disease, including the current topics about diagnosis and treatment, like provocation challenges and aspirin desensitization. We also discuss recent findings in the pathogenesis of the disease, as well as future trends in diagnosis and treatment, including monoclonal antibodies and a low salicylate diet as a treatment option.

1. Introduction

The aspirin-exacerbated respiratory disease (AERD) was described for the first time by Widal et al., in 1922. Later, in 1968, Samter and Beers integrated a clinical syndrome composed of bronchial asthma, nasal polyposis, and aspirin hypersensitivity, which came to be known as Samter's triad [1,2]. Nowadays, it is known that the chronic eosinophilic rhinosinusitis is part of the syndrome, and is considered a fourth hallmark of the disease. Disease exacerbations might be caused not only by aspirin ingestion, but also by other nonsteroidal anti-inflammatory drugs (NSAIDs) [3–6]; although certainly, in some cases, the disease can begin and progress in the absence of NSAIDs exposure [7–9].

Characteristically in AERD, the symptoms and signs are produced by pseudoallergic or non IgE-mediated reactions, and are frequently severe enough and difficult to treat, to consider the disease as an aggressive, life threatening, and chronic disorder [6,10–13].

This clinical syndrome has been called in several forms including Widal syndrome, aspirin triad, asthma triad, Samter syndrome, aspirin-sensitive rhinosinusitis/asthma syndrome, and aspirin-intolerant asthma; but currently the terms of Aspirin or NSAID Exacerbated Respiratory Disease (AERD/NERD) are preferred, to make emphasis on the upper and lower respiratory tract affection, since asthma is not always present in all the patients [4,14,15].

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ASA, acetylsalicylic acid; BAT, basophil activation test; CAST, cysteinyl-leukotriene release test; CT, computed tomography; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CRTH2, chemoattractant receptor homologous molecule expressed by Th2 lymphocytes; COX-1, cyclooxygenase 1; COX-2, cyclooxygenase 2; CysLTs, cysteinyl leukotrienes; CysLTR1, receptor of cysteinyl leukotrienes 1; CysLTR2, receptor of cysteinyl leukotrienes 2; EBC, eicosanoid profile in exhaled breath condensates; ECP, eosinophil cationic protein; EP2, E-prostanoid 2; EP2R, E-prostanoid 2 receptor; FCεRI, high affinity immunoglobulin E receptor; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FLAP, 5-lipoxygenase activating protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; H-PGDS, hematopoietic prostaglandin D synthase; ICU, intensive care unit; IFN, interferon; IL, interleukin; LMD, leukotriene modifiers drugs; L-PGDS, lipocalin-type prostaglandin D synthase; LT, leukotriene; LTC4S, leukotriene C4 synthase; MCP-1, monocyte chemoattractant protein-1; mPGES-1, microsomal prostaglandin E2 synthase 1; NSAIDs, nonsteroidal antiinflammatory drugs; NERD, NSAIDs exacerbated respiratory disease; PGE2, prostaglandin E2; PGD2, prostaglandin D2; PA2, phospholipase A2; SNPs, single nucleotide polymorphisms; S1P, sphingosine-1-phosphate; TARC, thymus and activation-regulated chemokine; Th1, T helper 1; Th2, T helper 2; TP, thromboxane prostanoid; TSLP, thymic stromal lymphopoietin; 15-HETE, 15-hydroxyeicosatetraenoic acid; 5LO, 5-lipoxygenase

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2. Epidemiology

The prevalence of AERD in the general population is about 0.3–2.5% [16–19]. However, the prevalence increases significantly in the asthmatic population, as has been estimated in 7.15% among adult asthmatic patients, and 14.89% among those with severe asthma [20]. The onset of symptoms may appear since the teenage years to 40 years of age, with an average age of 30 years [8,9,13,21]. AERD is more often reported in women than in men (57% vs. 43%). Most patients have a negative family history for AERD; only 1–6% of patients with the disease have a relative with the same condition [5,9,13,22]. No racial or ethnic predilection has been established [23,24].

3. Clinical features

3.1. Onset

AERD may appear most likely in people that have risk factors (female gender, young adulthood, genetic polymorphisms) who are exposed to determined triggers that lead to airway inflammation. Among the trigger factors that can drive to the first asthma attack in AERD patients are viral respiratory tract infections (45%), aspirin/NSAIDs intake (14%), and allergen or industrial products exposure (14%). Other factors that might be implicated are diesel exhaust and cigarette smoke exposure [8,13,24–28]. Nevertheless, in a survey with a European population, the precipitating factor of the first asthma attack remained unknown in 30% of the study patients [13]. Some reports have shown that atopy and positive skin test to common aeroallergens are present in 64–66% of AERD patients [8,9,29,30]. However in other surveys, the presence of atopy is reported only in 30–34% of the study subjects [13,23], being, in this case, close to the prevalence reported in the general European population, and clearly lower to the prevalence of atopy in asthmatic population without AERD [13,25,26].

3.2. Clinical course

The syndrome's clinical features are not usually present at once at the disease onset, most of the times they develop following a pattern (Fig. 1) [7]. The first clinical manifestation that usually appears in patients with AERD is rhinitis, which is referred as nasal congestion, nasal discharge, anosmia/hyposmia, and sneezing. Patients often describe having a cold that never goes away [4,8,9,13,31]. The presence of anosmia/hyposmia is so frequent (89%) and deep, that, in fact, a normal olfaction discards AERD [27]. The chronic rhinitis progresses to chronic hyperplastic eosinophilic sinusitis, a finding that can be observed in 99% of patients as hyperdensity in computed tomography (CT) [8,9]. The first manifestation of asthma appears at an average of 2 years

Table 1
Respiratory and non-respiratory manifestations after NSAID's intake in AERD patients.

Respiratory manifestations (42–88%)	Non-respiratory manifestations (8–20%)		
	Cutaneous (10–20%)	Gastrointestinal (18%)	Other (8–15%)
Nasal discharge and/or postnasal drip	Flushing	Nausea	Conjunctivitis
Nasal congestion	Pruritus	Vomiting	Headache
Hyposmia/anosmia	Rash	Diarrhea	Hypotension
Sinusitis	Urticaria		Loss of consciousness
Dyspnea/Cough	Angioedema		
Wheezing/Bronchospasm			
Laryngospasm			

after the onset of rhinitis, and the aspirin/NSAID intolerance tends to appear 4 years later [13]. Nevertheless, other studies have demonstrated that aspirin/NSAIDs hypersensitivity may appear at any time in the course of the disease [8,9]. Regarding nasal polyps, the moment of diagnosis is variable because it depends on the use of rhinoscopic examination [9,13,22]; therefore, this diagnostic procedure must be performed in any patient with suspicion of AERD, since nasal polyps, along with chronic rhinosinusitis, are the most common comorbid conditions associated with the disease [16].

3.3. Type of manifestations

Clinical manifestation after the administration of NSAIDs among patients with AERD can be divided in respiratory and non-respiratory (Table 1) [13,14,16,23,24,32–34]. Such reactions may appear from a few minutes, until 3 h, after the drug exposure [22,35]. Patients with severe respiratory reactions develop more frequently non-respiratory manifestations; however, in general, the intensity of the reactions is dose-dependent for each drug [4,7].

3.4. Complications

Asthma is categorized as severe in 59.4% of patients and uncontrolled in 18.9%–45.3% [18,36,37]. Chronic rhinosinusitis and asthma usually are refractory to typical treatment, and tend to get worse over time, even when avoiding NSAIDs [4,22,24,38–41]. Due to the chronic inflammatory process, patients with AERD may develop progressive fibrosis with airway remodeling [38,42]. Furthermore, approximately 50% of these patients are characterized by dependency of chronic oral corticosteroid therapy and a reduced lung function [9,12,23,38,43].

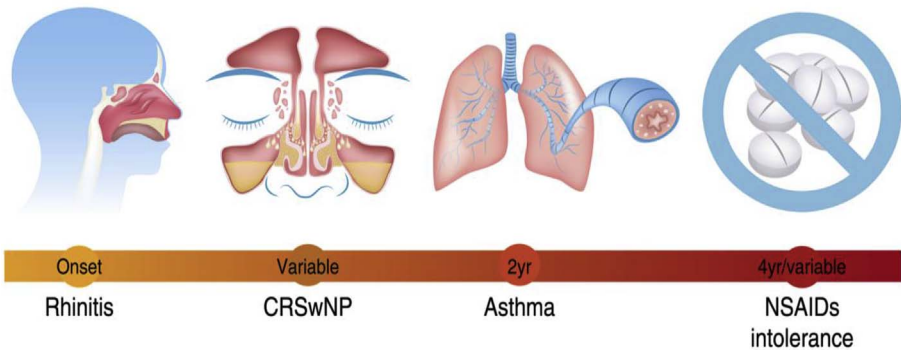


Fig. 1. Clinical course of AERD. The syndrome usually develops following a pattern; the first clinical manifestation is rhinitis, followed by chronic hyperplastic eosinophilic sinusitis. Asthma appears at an average of 2 years after the onset of rhinitis, and the aspirin/NSAID intolerance 4 years later; however, NSAIDs hypersensitivity may appear at any time in the course of the disease. Nasal polyps diagnostic time is variable depending on the use of rhinoscopic examination. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps.

The nasal polyps have an aggressive course and frequently regrow in a short period of time after polypectomy [11,23,44–46]. In fact, several complications have been reported because of the sinonasal polyps recurrence, like brain invasion, tympanic membrane perforation, recurrent sinus infection, and facial deformation due to the increased pressure in the bones of the nasal cavity and paranasal sinuses [23,47,48].

As mentioned before, acute exacerbations are commonly observed after the aspirin/NSAIDs administration in AERD patients. Some of these can be so severe that they may require intubation and mechanical ventilation. In a survey that included asthmatic patients who required mechanical ventilation, 25% were found to be aspirin intolerant [4,5,13,22,23,49]. Another complication, death from status asthmaticus in patients with AERD may occur during an NSAID-induced asthma exacerbation, but also during a viral infection, even without NSAIDs ingestion [14,50].

Although it is uncommon, patients with AERD may develop eosinophilia-associated coronary artery vasospasm; thus patients with AERD who develop symptoms of ischemic chest pain, should be screened for eosinophilia, since an early treatment with corticosteroids can be life-saving [51].

4. Cross reactivity and safety of NSAIDs in AERD

Patients with AERD typically experience cross-reactions to aspirin and NSAIDs with strong COX-1 inhibitory activity [8,27,29,52]. In a study of 300 patients with documented AERD in the United States, aspirin ingestion elicited typical respiratory reactions in 80%, ibuprofen in 41%, naproxen in 4%, and ketorolac in 1% of the study subjects [9]. Therefore, aspirin and strong COX-1 inhibitors are strongly contraindicated for patients with AERD.

On the other hand, acetaminophen is considered a weak COX-1 inhibitor, since low doses (generally below 500 mg) are safe for patients with AERD. However, at higher doses (> 1000 mg), acetaminophen can induce mild asthmatic reactions in 28%–34% of patients with AERD [8,29,52]. Such percentage may increase in another 6% when the dosage of acetaminophen is ≥ 1500 mg [8,29,53].

Meloxicam and nimesulide are preferably COX-2 inhibitors, and are usually well tolerated by patients with AERD when given at low doses. However, they can elicit mild respiratory reactions at higher therapeutic doses [8,29,52,54–57].

The COX-2 selective inhibitors, like valdecoxib and celecoxib, are generally well tolerated by patients with AERD [29]. Several single and double-blind placebo-controlled challenge studies have demonstrated that selective COX-2 inhibitors, given at therapeutic doses, do not cross-react with ASA or other NSAIDs in patients with AERD [58–64]. However, there have been reports in the literature on symptoms exacerbations after administering COX-2 selective inhibitors in AERD patients. Therefore, it has been suggested, by some experts, that the first full dose of a COX-2 inhibitor should be given in a physician's office or health facility [7,8,65]. Table 2 shows NSAID classification based in their ability to inhibit COX-1/COX2 isoenzymes [8,27,29,52].

Cross reactivity and symptoms exacerbations are not limited only to NSAIDs. In a study with 59 AERD patients, 83% reported respiratory reactions shortly after the ingestion of alcohol [66]. Interestingly, patients also reported alcohol tolerance after desensitization with acetylsalicylic acid (ASA) [67]. Even more, other worsening factors have been described in patients with AERD like the use of toothpaste (27%), as well as spearmint or peppermint flavored chewing gum, cow's milk (30%), and a salicylate rich diet [68].

Table 2
COX-1 and/or COX-2 isoenzymes inhibitors.

COX-1 inhibitors			COX-2 inhibitors	
Strong COX-1 inhibitors ^a		Weak COX-1 inhibitors ^b	Preferably COX-2 inhibitors ^c	Selective COX-2 inhibitors ^d
ASA	Meclofenamate	Salsalate	Celecoxib	Meloxicam
Benoxaprofen	Metamizole	Acetaminophen	Etoricoxib	Nimesulide
Diclofenac	Mefenamic acid	(at doses > 1000 mg)	Lumiracoxib	
Diflunisal	Nabumetone		Parecoxib	
Etodolac	Naproxen		Valdecoxib ^e	
Fenoprofen	Naproxen		Rofecoxib ^e	
Flurbiprofen	Oxaprozin			
Ibuprofen	Piroxicam			
Indomethacin	Sulindac			
Ketoprofen	Tolmetin			
Ketorolac				

^a May inhibit COX-2 at high concentrations.

^b No COX-2 inhibition.

^c Partially inhibit COX-1 at higher dose.

^d No inhibition of COX-1 at the prescribed doses.

^e Removed from worldwide market due to safety concerns.

5. Pathogenesis

5.1. Generalities

The exact mechanisms of pathogenesis in AERD are not fully understood [15,24,69], but genetic and environmental factors participate in the development of the disease [7,25,70–72]. It is known that alterations in arachidonic acid metabolism [6,7,12,40,43] may induce an imbalance between pro-inflammatory and anti-inflammatory substances, expressed as an overproduction of cysteinyl leukotrienes (CysLTs), and an underproduction of prostaglandin E2 (PGE2) [15,73–80]. A key feature of AERD is the presence of eosinophilic infiltrates in the respiratory tract; however, the activity of other cells like neutrophils, basophils, monocytes, macrophages, mast cells, T-cells, and platelets has been demonstrated in several studies [6,76,81–89].

5.2. Cysteinyl leukotrienes

CysLTs exert an important pro-inflammatory and pro-fibrotic effect on the respiratory tract. They induce bronchoconstriction, mucus secretion, eosinophilic inflammation and vascular leak through the interaction with their specific receptors [12,73,80,90]. AERD patients have an elevated expression of CysLTs receptors (CysLTR1 and CysLTR2) in mucosal tissue, compared with aspirin tolerant patients [78,91,92]. Also there is an increased expression of leukotriene C4 synthase (LTC4S), an enzyme that participates in CysLTs production in AERD [75,76,80,89]. Even more, a disturbance in platelet-leukocyte interactions may probably contribute to the overproduction of CysLTs [81,87].

5.3. Prostaglandin E2

Prostaglandin E2 (PGE2) is produced in a large amount during inflammation by COX2 coupled with microsomal PGE2 synthase 1 (mPGES-1) [93–95]. This molecule exerts a variety of anti-inflammatory effects through the E-prostanoid 2 (EP2) receptor [96,97], such as inhibition of mast cell degranulation, inhibition of eosinophils activation, modulation of platelet aggregation, inhibition of 5-

lipoyxygenase (5LO) function (enzyme that catalyzes the transformation from arachidonic acid to CysLTs). PGE₂ also prevents smooth muscle contraction, vasodilatation, and increased vascular permeability [12,98–102]. Patients with AERD have diminished levels of PGE₂, COX2, and EP2 receptors in fibroblasts and sinonasal tissue; as well as low levels of EP2 receptor in neutrophils, mast cells, eosinophils, and T-cells, compared with aspirin tolerant patients. It has also been described a possible resistance of granulocytes to PGE₂, which in turn would promote a persistent inflammatory status characteristic of AERD [76–78,96,103,104].

5.4. Prostaglandin D₂

PGD₂ is a structural isomer of PGE₂. Two enzymes are identified to produce PGD₂ called hematopoietic prostaglandin D synthase (H-PGDS) and lipocalin-type (L-PGDS). H-PGDS is involved in the production of PGD₂ in mast cells and other related tissues, particularly at high levels in persons with AERD, at baseline and (especially) during reactions; while L-PGDS is mostly expressed in the central nervous system [105]. PGD₂ activates eosinophils, basophils, and lymphoid helper cells through chemoattractant receptor homologous molecule expressed on Th2 lymphocytes (CRTH2), and elicits bronchoconstriction at least in part through the interaction with thromboxane prostanoid (TP) receptor [12,106]. Urinary PGD₂ levels have been found to correlate with nasal polyp thymic stromal lymphopoietin (TSLP) mRNA expression in patients with AERD and increase during clinical reactions, reflecting mast-cell activation [107]. Interestingly, Cahill et al. demonstrated that high-dose aspirin reduced levels of PGD₂ metabolites in urine suggesting an important role of PGD₂ in AERD [108].

5.5. Cytokine expression

Most studies have shown a cytokine milieu consistent with Th2 immunity; however, recent studies suggest that AERD may represent a “mixed” Th1/Th2 profile with prominent expression of IFN- γ [6,15]. There are data supporting the fact that IFN- γ and IL-4, but not IL-5 or IL-13, are upregulated in AERD polyp tissue and are derived from eosinophils [6,109,110]. Both IL-4 and IFN- γ increase the expression of LTC₄S in mast cells and eosinophils progenitors, respectively [109,111]. Also, IL-4 and IFN- γ may increase the expression of CysLTR1 and CysLTR2 in mononuclear cells and granulocytes [112,113]. Additionally, IL-4 decreases the expression of COX2 and mPGES-1 in monocytes [114]. We have recently shown increased levels of IL-16 and Thymus and Activation-regulated Chemokine (TARC) in nasal lavages derived from AERD patients [115].

IL-33 and TSLP are cytokines of innate type 2 immune response. They can promote mast cell activation, contributing to AERD pathogenesis [107,116]. Among the different mechanisms involved in the disease, it has been proposed that CysLTs increases the expression of IL-33 and TSLP from structural cells, which in turn will stimulate the mast cells to produce PGD₂ [86,108,116–118]. The increase in PGD₂ will result in enhancement of the inflammatory process and the symptoms in AERD, as mentioned before, through the interaction with, CRTH2 and TP receptor [12]. See Fig. 2 for the mechanisms of disease.

5.6. Genetic expression

Different studies have shown that several polymorphisms, human leukocyte antigen (HLA), single nucleotide polymorphisms (SNPs), and methylation patterns are associated with the presence of AERD in different populations [25,26,71,72,119,120]. Such association is so consistent that the detections of the genes CNKSR3 and SPTBN2, expressed

in peripheral blood mononuclear cells, could be used as an efficient method for predicting AERD development in selected patients [121].

6. Diagnosis

The diagnosis of AERD is suspected in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and a history of typical respiratory reactions to NSAIDs; however, it is only confirmed after a positive provocative challenge with aspirin/NSAIDs [14,16].

Even when a provocative challenge test is no available in most health facilities, knowing the antecedents combined with a scrupulous physical examination can be very helpful to achieve a proper diagnosis. For example, 42% of patients with CRS, nasal polyps, and asthma, even without former NSAIDs intolerance, will result with a positive oral aspirin challenge. This percentage increases to 86% when a prior history of a single reaction to NSAIDs has been documented, and up to 90% if two or more reactions to NSAIDs have been reported [14,16,122].

6.1. Provocation challenges

The gold standard for diagnosis of AERD is a provocative aspirin challenge [17,123]. There are four types of provocation challenges depending on the route of administration: oral, bronchial inhalation, nasal inhalation, and intravenous administration [8,17,29,43,124]. Any of these tests must be performed based on three general indications: suspicion of AERD based on a history of typical respiratory symptoms after ingestion of COX-1 inhibitors, suspicion of AERD based on clinical presentation (e. g. asthma, CRS, and/or nasal polyps) despite the lack of a clear history of NSAIDs intolerance, and as part of the aspirin desensitization process [52].

The tests can be performed in an outpatient or inpatient setting; the patient should be in stable clinical condition, and with FEV₁ of at least 60% of the predicted value [17,34,52,125]. Emergency resuscitative equipment should be readily available for the risk of severe reactions, and the challenges have to be carried out under the direct supervision of a physician and skilled personnel [34,52,125]. Some asthma controlling drugs, like antihistamines and short-acting inhaled β agonists or anticholinergics, are discontinued 24 h before challenge; however, to prevent airways hyperreactivity, patients must be instructed to continue their prescriptions with oral corticosteroids (≤ 10 mg per day of prednisolone), topical corticosteroids, leukotriene modifying drugs, and long-acting bronchodilators [52].

The oral challenge is the most commonly performed, because it simulates the natural exposure and only a spirometer is required [24,43,52]. This test should not be performed in patients with a history of severe reactions to NSAIDs; neither in patients with serious and uncontrolled illness like heart, digestive tract, liver, and/or kidney disease. The aspirin challenge should be avoided also in those who have suffered a respiratory tract infection within four weeks prior to the challenge, in pregnancy, and in those under treatment with β -receptor blockers [125]. The test is considered positive if FEV₁ declines 20% or more from the baseline value. After the aspirin challenge, the development of unequivocal symptoms like nasal congestion, rhinorrhea, ocular injection, and/or periorbital swelling can also be considered as a positive result, even if the patient does not present bronchospasm or the previously mentioned FEV₁ decline [34,43,52,125]. If the FEV₁ does not decrease $\geq 20\%$, and/or symptoms do not appear 3 h after the 325 mg dose, the challenge is considered negative. The limitations of this route are the risk of severe reactions, time-consuming (two or three days), and the requirement of highly-trained personnel [17,52,126,127]. Table 3 shows a representative protocol of the Oral Aspirin provocation challenge [7,17,126].

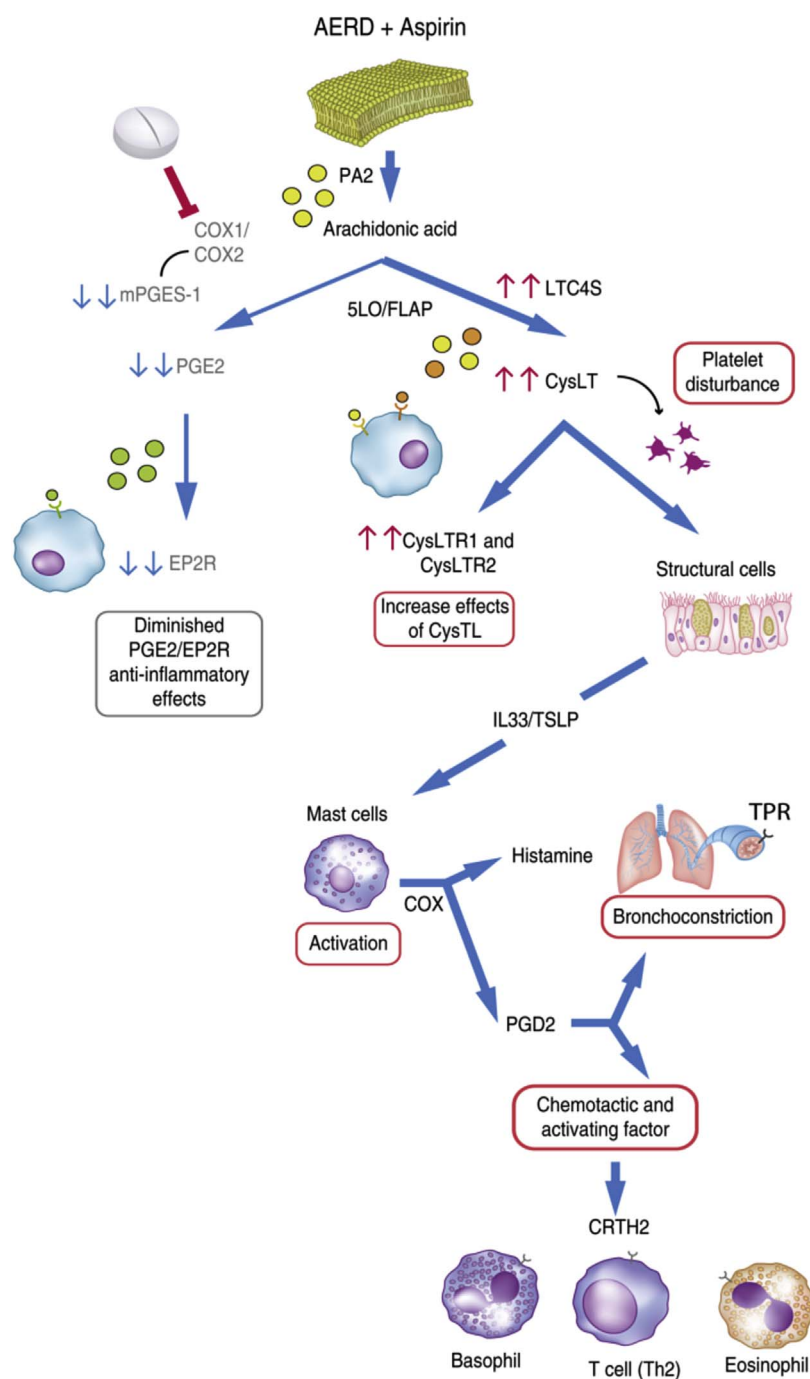


Fig. 2. Mechanisms of pathogenesis in AERD. Alterations in arachidonic acid metabolism may induce an imbalance between pro-inflammatory and anti-inflammatory substances, with an over production of CysLTs, IL-33/TSLP and PGD2, leading to the classical disease exacerbations, after Aspirin/NSAIDs administration. Abbreviations: AERD, aspirin exacerbated respiratory disease; COX-1 and -2, cyclooxygenases-1 and -2; EP2R, E-prostanoid 2 receptor; CRTH2, chemoattractant receptor homologous molecule expressed by Th2 lymphocytes; CysLTs, cysteinyl leukotrienes; CysLTR1 and 2, cysteinyl leukotrienes receptor 1 and 2; 5LO, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; LTC4S, Leukotriene C4 synthase; mPGES1, microsomal PGE2 synthase 1; PA2, phospholipase A2; PGE2, prostaglandin E2; PGD2, prostaglandin D2; TPR, T prostanoid receptor; TSLP, thymic stromal lymphopoietin.

The oral provocation test can be replaced with bronchial or nasal aspirin challenges [34,125]. The bronchial challenge is performed with lysine-aspirin, which is supplied to the study subject using a nebulizer [125]. This test is safer, faster, and takes less time to perform (< 4 h) than the oral challenge [22,52]; but it requires special equipment and can be used only in patients with bronchial reactions [34]. A positive reaction is considered if FEV1 decreases 20% or more from the baseline value, or in those patients who develop strong extrabronchial symptoms. As previously mentioned in the oral challenge, a negative

reaction is considered when the maximum cumulative dose of lysine-aspirin is reached without the presence of adverse symptoms [52,125].

The nasal route also uses lysine-aspirin, but this can be replaced by a ketorolac-solution [34,52]. Nasal challenge is considered in patients that were unsuitable to undergo oral or bronchial challenges, since it can be used in patients with unstable or severe asthma, because it rarely produces systemic reactions, therefore, it can be performed in outpatients settings [22,34,52,125,128]. However, this test requires special equipment (rhinomanometer) and must be avoided in patients with

Table 3
Oral Aspirin provocation challenge.

Indications	Contraindications
-Suspicion of AERD based on a history of respiratory symptoms after ingestion of NSAID	-Patients with a history of severe reactions to NSAIDs
-Suspicion of AERD based on clinical presentation (e. g. asthma, CRS, and/or nasal polyps) despite the lack of a clear history of NSAIDs intolerance	-Patients with serious and uncontrolled illness like heart, digestive tract, liver, and/or kidney disease or pregnancy
-As part of the aspirin desensitization process	-Patients with respiratory tract infections within four weeks prior to the challenge

Before challenge:

- ✓
The patient must stop β -blockers and ACE inhibitors
- ✓
Placebo challenge can be conducted a week before challenge or if the patient's baseline FEV1 is the same as a previous best value and the patient has not required his or her albuterol in the past week, then placebo challenge can be skipped
- ✓
FEV1 should be at least 1.5 L and > 60% of predicted value

Protocol:		
Time	Day 1	Day 2
0 h	20–40 mg†	100–160 mg
3 h	40–60 mg	160–325 mg
6 h	60–100 mg	325 mg*
-Measure FEV1 every hour and wait 3 h between doses		

-Possible outcomes or reactions:

- I. Naso-ocular alone
- II. Naso-ocular and a 15% or > decline in FEV1
- III. Lower respiratory reaction only (FEV1 declines by > 20%)
- IV. Laryngospasm with or without I, II, III
- V. Systemic reaction: hives, flush, gastric pain, hypotension

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

ACE, Angiotensin-converting-enzyme; FEV1, forced expiratory volume in 1 s.

Table 4
Sensitivity and specificity of the different routes for aspirin provocation challenge.

	Sensitivity	Specificity
Oral challenge	80%–89%	93%
Bronchial challenge	77%–90%	93%
Nasal challenge	38%–88%	84%–96%

nasal obstruction or turbulent nasal flow [34]. According to that, any pathology of the nasal cavity, such as septum perforation or massive nasal polyposis, is a contraindication to this procedure [125]. A positive response is defined as the appearance of nasal symptoms such as rhinorrhea, nasal congestion or sneezing, as well as a 25% drop of the total nasal flow compared to a baseline value measured by acoustic rhinometry; or a 40% bilateral decrease of inspiratory nasal flow compared to a baseline value, assessed with rhinomanometry or a peak nasal inspiratory flowmeter [52,125].

A survey reported that 14%–16% of patients with a positive history for AERD had a negative oral challenge [122]. This result does not exclude AERD because it may reflect either development of silent desensitization (likely induced by the concurrent use of leukotriene modifying drugs and subthreshold aspirin dosing), or blocking effects of other medications used to control chronic inflammatory diseases. In these particular cases, the patients could have a well-controlled underlying disease over a long period of time [14,34,129].

The sensitivity and specificity of the different routes vary in the

literature (Table 4) [34,125,130–132]. In general, the oral challenge is considered to have the best performance and predictive value, so a negative response to nasal or bronchial provocation test should be followed by oral aspirin challenge if clinical suspicion remains [22,52,125,128].

6.2. Other diagnostic methods

CRS and nasal polyps can be identified by CT, x-ray, rhinoscopy, or nasal endoscopy [7,34]. Since AERD is not an IgE-mediated reaction, skin prick test using NSAIDs are useless [133].

There are several tests that could act as tools to detect abnormalities in inflammatory pathways and gene expression. These tests can be performed with biological materials, like blood, urine, sputum, or exhaled air [34]. However, they still require more validation and have less sensitivity and specificity when compared with the provocation challenges [8,34,124]. Some of these promissory assays are shown in Table 5.

7. Treatment

Once the diagnosis of AERD is made, the possibilities of treatment encompass non-pharmacological treatment, drug therapies, surgical interventions, aspirin desensitization, and monoclonal antibodies [6,7,69].

7.1. Non-pharmacological treatment

This form of treatment consists mainly in patient education and counseling to strictly avoid COX-1 inhibitors, with the identification of well-tolerated alternative drugs for the management of other comorbidities [7,16]. However, COX-1 inhibitors avoidance is difficult to maintain because they are frequently used for the treatment of several diseases. Even more, it is important to notice that most patients will develop progressive airway and sinus disease, even if they elude the use of NSAIDs [7].

The diet can be considered as another non-pharmacological treatment. A low salicylic acid diet has been explored as a therapeutic intervention in these patients. In some studies, the elimination in the diet for 6–12 weeks of food containing salicylates like fruits, vegetables, herbs, spices, almonds, and several oils improved the nasal symptoms and nasal endoscopy findings of individuals with AERD [69,147–149]. Table 6 shows a list of food containing high, intermediate, and low levels of salicylic acid; in general, food with high and even intermediate salicylates level should be avoided in highly sensitive patients [150,151]. Besides, the effect of high omega-3 and low omega-6 fatty acids in the diet is being evaluated [152], based on the assumption that an increase in dietary omega-3 fatty acids may lead to a rise in metabolic products of eicosapentaenoic acid, which exert less inflammatory biologic activity than those obtained from the metabolism of omega-6 fatty acids [69,153].

7.2. Pharmacological treatment

Intranasal saline irrigation. Rinsing the nasal cavities with saline solution and saline nasal sprays has demonstrated to be helpful as adjunctive treatment for CRS. This simple procedure reduces nasal or sinus drainage, removes secretions, and washes away allergens and irritants; improving the response to topical corticosteroids, the reason why the nasal saline irrigation is recommended immediately prior to the administration of other medications [7]. The physiological saline solution is better than the hypertonic saline solution on mucociliary

Table 5

Promissory AERD diagnostic test and biomarkers.

Diagnostic test	Sensitivity (%)	Specificity (%)	Source
-Basophil Activation Test (BAT)	16.7–80	34–100	[34,134,135]
-Detection of 15-HETE from nasal polyp epithelial cells, and peripheral blood leukocytes	63–82	50–83	[34,136,137]
-Cysteinyl-leukotriene Release Test (CAST) from peripheral blood leukocytes	25	92	[34,138]
-Fractional exhaled nitric oxide (FeNO), after aspirin ingestion	90	100	[139]
-Detection of urinary LTE4 in high levels	55–81	79–82	[34,140]
-Sputum detection after aspirin challenge of increased levels of PGD2, LTD4, LTE4, and diminished levels of PGE2 and LTB4	N/A	N/A	[141]
-Measurement of eosinophil levels in blood, sputum, and nasal mucus	N/A	N/A	[124]
-Eicosanoid profile in Exhaled Breath Condensates (EBC)	N/A	N/A	[142]
-Increased levels ECP, GM-CSF, and MCP-1 in sinonasal tissue	N/A	N/A	[143]
-Increased level of serum sphingosine1-phosphate (S1P), and urinary sphingosine	N/A	N/A	[144]
-Increased levels of IL-16, TARC, and periostin in nasal lavages	N/A	N/A	[115]
-Specific IgE against <i>S. aureus</i> enterotoxins, in nasal polyp tissue	N/A	N/A	[145,146]
-Microarray analysis to identify genetic expression of cytokines, and detection of genes associated with the presence or development of AERD (rs3128965, CNKSR3 and SPTBN2)	N/A	N/A	[34,119,121,143]

N/A, not available; 15-HETE, 15-Hydroxyeicosatetraenoic Acid; ECP, eosinophil cationic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; MCP-1, and monocyte chemoattractant protein 1; TARC, thymus and activation-regulated cytokine.

Table 6

Food levels of salicylic acid.

Food levels of salicylic acid ^a			
	High	Intermediate or variable	Low
Vegetables	Alfalfa, broccoli, chicory, peas, radish, romaine lettuce, tomatoes (dried)	Artichoke, beetroot broccoli (cooked), brussels sprouts, butterhead lettuce, cauliflower, chard, cherry tomato (fresh), chili pepper, cucumber, eggplant, garlic, ginger root, mushrooms, olives, onion, pepper, pickled cucumbers, potatoes, pumpkin, romaine lettuce, spinach, tomatoes, Zucchini	Asparagus (Green), beetroot, beans, cabbage, carrot, celery, iceberg lettuce, lentils, soybeans
Fruits	Apple (dried), Avocado, blueberry, boysenberry, cranberry, currant, guava, lingonberry, loganberry, peach (dried), pineapple, raisins, raspberries, strawberry (dried)	Apple (fresh), apricot, blackberry, cherry, fig (dried), grapes, kiwi, lemon, mandarin, mango, nectarine, orange, passion fruit, peach, pear, pomegranate, watermelon	Lime, pawpaw, banana, fig, grapefruit, pear (canned)
Herbs, spices and condiments ^b	Allspice, bay leaf, cinnamon, cloves, cumin. Fenugreek, garlic powder, ginger, mint, mustard, oregano, paprika, rosemary, tamarind, thyme, vanilla	Basil, hummus, honey, mint vinegar, peppermint, tabasco sauce, Worcestershire sauce	Cocoa powder, coriander, dextrose, parsley, saffron, salt, soy sauce
Drinks	Apple juice, cranberry juice, orange juice, pineapple juice, root beer	Beer, coca cola, coffee, tea, wine	Rum, tequila, vodka, whisky
Cereals		Maize	Barley, oats, rice, rye, wheat
Seeds	Almonds, macadamia nuts, peanuts, pine nuts, pistachio nuts	Coconuts, hazelnuts, pecan nuts, sesame seed, sunflower seed, walnuts	Cashew nuts
Other meals		Sobrassada	Meat (beef, lamb, pork), poultry, fish, eggs, dairy products

^a Salicylate levels in food may present a considerable variation depending on the origin, growing conditions, processing, and/or storage.

^b Some foods like spices and condiments, contain high levels of salicylate per 100 mg; however, as they are usually consumed in small amounts, their clinical effects may be low or negligible, depending on every individual sensitivity.

clearance and nasal patency. The saline irrigation provides greater benefits than saline nasal sprays, in terms of severity and frequency of the symptoms and quality of life improvement; besides, nasal irrigation is a most efficient method for delivery [154].

Intranasal corticosteroids. These medications must be considered as a first-line therapy in patients with AERD [7]. They are widely used as maintenance treatment for patients with CRSwNP, because they have shown to be highly effective in reducing nasal and sinus inflammation, as well as the size and formation of new polyps, and the intensity of rhinitis symptoms. Also, intranasal corticosteroids can prevent the relapse and regrowth of nasal polyps after surgery [7,16,154,155].

Leukotriene modifiers drugs (LMD). Leukotriene receptor antagonists, like montelukast, zafirlukast, pranlukast, and 5LO inhibitors, as zileuton, have shown to be effective in the management of patients with AERD because overproduction of CysLTs is a key feature in the pathogenesis of the disease [6,156,157]. Both, montelukast and zileuton, have shown a decrease in asthma symptoms, a reduced frequency in the

use of bronchodilators, improvement of pulmonary function evaluated through FEV1, and an increase in quality of life [158,159]. Leukotriene receptor antagonists are more frequently used than 5LO inhibitors, because they are less expensive and have fewer side effects [6].

Oral corticosteroids. If symptoms persist despite the therapies mentioned above, oral corticosteroids may be considered to reduce overall mucosal edema and nasal polyp tissue [7]. In most cases, this alternative results in significant symptoms improvement, and its maximum effect is reached in 2–3 weeks after the treatment was initiated, although the response varies widely among patients [7,160]. The prescription of oral corticosteroids requires careful consideration because of the potentially devastating adverse effects associated with their use, so they should not be used as first-line therapy [160]. If the patients do not have a clinical benefit with the use of oral corticosteroids, as for example, a significant reduction in polyps size or improvement of anosmia, sinus surgery should be considered [7].

Inhaled corticosteroids with bronchodilator therapy. Asthma

Table 7
Medications currently used for the treatment of AERD.

Medication	Mechanism of action	Clinical efficacy	Reference
Intranasal corticosteroids (budesonide, fluticasone, mometasone, triamcinolone, beclomethasone, flunisolide, ciclesonide)	Phospholipase A2 inhibition in the arachidonic acid pathway	Reduce nasal and sinus inflammation, as well as the size and formation of new polyps. Also, they can prevent the relapse and regrowth of nasal polyps after surgery	[16,40,155,161]
Leukotriene modifiers drugs (montelukast, zafirlukast, pranlukast)	Blockade of CysLTR1	Decrease asthma symptoms, reduce the use of bronchodilators, improve pulmonary function evaluated through FEV1, and increase the quality of life	[6,157,158]
Zileuton	Impairs leukotriene production by 5LO inhibition	Decreases asthma symptoms, reduces the use of bronchodilators, improves pulmonary function evaluated through FEV1, and increases the quality of life	[6,157,159]
Oral corticosteroids	Phospholipase A2 inhibition in the arachidonic acid pathway	Reduce overall mucosal edema and nasal polyp tissue, resulting in significant symptoms improvement. The response varies widely among patients	[7,160,162]
Inhaled corticosteroids with bronchodilator therapy (short-acting and long-acting β 2-agonists)	Corticosteroids: Phospholipase A2 inhibition in the arachidonic acid pathway β 2-agonists: induce bronchial smooth muscle relaxation	These drugs are used for the asthma management. Decrease disease activity, and reduce the need for systemic corticosteroids	[7,160]
Aspirin (used within a desensitization protocol)	Impairs prostaglandins production by COX-1 inhibition (may inhibit COX-1 at high concentrations)	Improves the quality of life, nasal and asthma symptoms scores, as well as the sense of smell. Reduces the frequency of polyp formation, the episodes of sinusitis, and the need of systemic corticosteroids	[163–167]

CysLTR1, cysteinyl leukotrienes receptor 1; 5LO, 5-lipoxygenase.

management in AERD must include inhaled corticosteroids with or without short-acting and long-acting β 2-agonists, and/or other therapeutic strategies, based on current asthma management guidelines. These inhaled drugs remain as important options to decrease disease activity, and reduce the need for systemic corticosteroids in patients with AERD [7].

Other considerations. It is important to consider that patients with AERD often have other comorbidities, which may contribute to upper and lower airway inflammation, for example, allergic rhinitis, underlying infectious sinusitis, and gastroesophageal reflux disease. These and other comorbidities should be properly treated to achieve a maximum control of the disease [7]. Table 7 summarizes the mechanism of action and clinical efficacy of medications currently used for the treatment of AERD.

7.3. Surgery

Sinus surgery to treat CRSwNP should be considered when medical treatment fails [16]. The goals of surgery are the improvement of nasal obstructive symptoms with reduced rhinorrhea and postnasal discharge; the achievement of a stable and sustained improvement of smell; and finally, a better control of bronchial asthma [168]. The surgical procedures most frequently used are polypectomy, endoscopic sinus surgery, and ethmoidectomy [7]. Nowadays, endoscopic sinus surgery is the preferred method, because of its proven safety and lower morbidity [168–170]. The surgical goals of nasalization are the eradication of the ethmoidal mucosa and the creation of a cavity as wide as possible to facilitate subsequent cleaning and proper dissemination of topical nasal steroids [168]. In AERD patients, CRSwNP exhibits a tendency to recur after surgery, up to 10-fold higher than that reported in patients with other forms of CRSwNP [16,171].

It is important to note that surgery does not affect the underlying inflammatory component of the disease and, therefore, medical treatment is still necessary after surgery [7]. This is the reason why aspirin desensitization is frequently used as a follow-up treatment after surgery, because it decreases the likelihood that AERD patients will require an additional surgical intervention in the following 2 years [7,172].

7.4. Aspirin desensitization

Aspirin desensitization treatment is an option to decrease disease

activity [164]. Multiple studies have shown several benefits, like improvement in the quality of life, improvement in nasal and asthma symptoms scores, as well as in the sense of smell. This treatment can also reduce the frequency of polyp formation, the episodes of sinusitis, and the need of systemic corticosteroids [7,164–166]. Aspirin desensitization is effective in reducing important markers of disease activity in AERD patients [165,166].

The use of LMD as pretreatment enhances the safety of oral aspirin challenge followed by aspirin desensitization in patients with AERD, by significantly decreasing the degree of asthmatic responses [173]. It has been suggested that the administration of LMD should be started at least one week prior to the oral challenge [7]. In a study with 420 patients with suspicion of AERD, who underwent oral aspirin challenge and desensitization, 9% of them suffered a large FEV1 decrease (> 30%), and 20% presented a moderate FEV1 decrease (21%–30%). The risk factors associated with such an important reduction in the respiratory capacity were the lack of LMD use, a baseline FEV1 of less than 80% of the predicted value, and previous asthma-related emergency department visits [127]. In the same survey, 75% of patients reacted to aspirin with a low provocative dose of either 45 or 60 mg [127].

The rate of adverse side effects from aspirin therapy ranges between 8 and 23%, depending on the study and the dose of aspirin used [7]. During the desensitization process, the most important complications are severe asthma attacks. A research group reported that only two patients had to be moved to the intensive care unit (ICU) because of severe asthma attacks, from over 800 patients that underwent aspirin desensitization. Despite the small proportion of patients requiring the ICU, its availability is strongly recommended when the desensitization protocol is performed [37].

Desensitization protocols. Several aspirin desensitization protocols have been described in the literature [7]. The Aspirin Desensitization Joint Task Force recommends a protocol that starts with an oral aspirin challenge, giving 20.25 mg of aspirin by mouth followed by 40.5, 81, 162.5 and 325 mg at 90 min intervals. They suggest to measure the FEV1 and to perform a clinical evaluation, at least every 90 min. When the provoking dose is tolerated, dose escalation may continue. A persistent decrease in FEV1 $\geq$ 15%, with or without other associated symptoms, lasting longer than 3 h despite therapy, is an indication to discontinue the desensitization process for the day. The second day of the desensitization process can be initiated by repeating the last

Table 8
Aspirin desensitization treatment.

Candidates for aspirin desensitization	Contraindications for aspirin desensitization	
-Poorly controlled symptoms despite standard therapies	-Pregnancy	
-Recurrent sinus disease with polyp regrowth after resection	-Unstable asthma	
-Frequent use of systemic corticosteroids	-Gastrointestinal ulcers	
-Indication for aspirin or NSAIDs to treat comorbid diseases	-Bleeding disorders	
Protocol:		
Time	Day 1	Day 2
0 h	20.25 mg	81 mg
1.5–3 h	40.5 mg	162.5 mg
3 to 6 h	81 mg	325 mg $\frac{1}{2}$
-Measure vital signs every hour during desensitization, then as needed		
-Obtain baseline FEV ₁ by spirometry; precalculate a 20% reduction in FEV ₁ by multiplying FEV ₁ in liters by 0.8		
-Obtain spirometry (FEV ₁) before each aspirin dose, every hour, and as needed; if severe shortness of breath or if FEV ₁ decreases by > 20%, give nebulized albuterol and notify physician		
-If systolic BP is < 90 mm Hg, give epinephrine 1:1000 0.3 mL intramuscular and notify physician		
-Rhinitis, nasal congestion, flushing: check FEV ₁ and BP; if rhinitis is accompanied by a decrease in FEV ₁ by 20% or if systolic BP is < 90 mm Hg, treat as above and notify physician: for rhinitis, nasal congestion or flushing alone, give diphenhydramine 50 mg IV and notify physician		
Discharge indications:		
-Two aspirins 325 mg by mouth, b.i.d.		
-Consider a proton pump inhibitor or H ₂ blocker for gastric lining protection		

FEV₁, forced expiratory volume in 1 s.

tolerated dose. The desensitization procedure can be continued as indicated herein, until the goal of tolerating 325 mg of aspirin is reached. Most individuals will take 2 days to complete the desensitization procedure [174]. The optimal maintenance dose of aspirin is unknown, but the best symptom control has been with 650 mg twice a day, with a response rate of 69% [7,164,166,175]. Therefore, aspirin is typically given at 650 mg twice daily after initial desensitization for the first month, but if the patient achieves improvement, the maintenance dose can be tapered down to 325 mg twice daily. The desensitized state can be maintained with as little as 81 mg for patients who only need cardiovascular disease prophylaxis [174,175]. However, in a survey, most patients with AERD referred return of nasal congestion and other symptoms, when their daily aspirin dose was diminished to less than 325 mg twice daily [175]. If a brief interruption in aspirin therapy occurs, less than 48 h, aspirin may be restarted at the maintenance dose. If the interruption is greater than 48 h, the recommendation is to repeat the desensitization protocol [17,164].

The aspirin desensitization treatment is an effective add-on therapy, with a responding rate of 87% in patients with AERD [164]. Table 8 shows the main indications and contraindications for the aspirin desensitization treatment, as well as a proposed protocol based on recommendations of several researchers, and The Aspirin Desensitization Joint Task Force [7,17,69,126,167,174,176].

Silent desensitization. White et al. described a series of patients with a high suspicion of AERD, but with a negative aspirin challenge. After a second challenge with a higher dose of aspirin and without pretreatment with LMDs, antihistamines, and oral corticosteroids for at least 1 week, these patients subsequently proved to have AERD. Therefore, the authors suggest that even when silent desensitization is an uncommon event, clinicians performing aspirin desensitization should understand that this can occur and they must consider a second confirmatory aspirin challenge in some patients [7,129].

7.5. Monoclonal antibodies

As in other diseases, monoclonal antibodies represent a potential and promising therapy in AERD; some are in development or have been approved for several related clinical conditions [6].

Omalizumab. This is a humanized recombinant monoclonal antibody that blocks the binding of IgE to its high affinity receptor (FcεR1) [177]. The mechanism by which omalizumab is effective in AERD is unclear, since the disease is not IgE-mediated [69,178], but it has been shown to reduce the biomarkers of disease activity [179]. Some authors report the effectiveness of omalizumab to improve the quality of life, the symptoms and lung function in patients with AERD [177,179,180]. In a study performed in Japan in 2016 and a survey performed in USA in 2015 in patients with AERD, 52% and 57%, respectively, showed or referred improvement after the treatment with omalizumab. On the other side, there is a report on eight patients treated with omalizumab and had a positive oral aspirin challenge; suggesting that omalizumab does not block aspirin reactions in patients with AERD [68,69]. The use of omalizumab in AERD requires further studies to identify its mechanism of action and determine its efficacy and cost-effectiveness in that population [69].

Other monoclonal antibodies, now in development for others diseases, could be especially effective in AERD [7]; mepolizumab, reslizumab, benralizumab, and dupilumab are good examples.

Mepolizumab, reslizumab, and benralizumab. These are anti-IL-5 monoclonal antibody approved for severe eosinophilic asthma. Studies have shown that they can decrease the nasal polyps size [6,7,181].

Dupilumab. Is an IL-4α receptor antagonist that blocks IL-4 and IL-13 signaling. In clinical trials, it has shown benefits in patients with moderate to severe eosinophilic asthma, decreasing the number of exacerbations, improving their lung function, as well as the nasal symptoms, and reducing the levels of Th2-associated inflammatory markers [69,182]. However, until now, it has not been studied specifically for AERD [69].

Other agents in development for asthma that could have clinical utility in AERD, include the anti-IL-13 monoclonal antibodies, lebrikizumab, tralokinumab, and GSK679586; as well as the anti-IL-17 brodalumab and ixekizumab, which are under investigation for psoriasis and psoriatic arthritis [7].

7.6. Allergen immunotherapy

This therapy has not been formally investigated specifically for AERD. Therefore, it is not recommended as a standard treatment [69]. However, since many patients with AERD have atopy as a comorbid condition, the immunotherapy can be prescribed to those who experience obvious periodic or perennial allergic signs and symptoms [69,183]. However, in a survey of patients with AERD, who were under allergen immunotherapy, 62% did not find it effective, 30% found it somewhat effective, and only 8% found it extremely effective [68,69].

7.7. Other therapies under research

Several drugs may show, in the future, promising results in the treatment of AERD. Current trials are investigating platelet-targeted therapies, including a P2Y₁₂ receptor antagonist, which inhibits platelet activation and aggregation, decreases pulmonary inflammation, and reduces the severity of aspirin reactions during aspirin challenge. There is also under investigation a thromboxane receptor antagonist (ifetroban), which can block the signal that induces bronchoconstriction [69]. PGD₂ acts through CRTH2 activating and recruiting effector cells on respiratory tissues in AERD; currently, several CRTH2 antagonists are in development for asthma and allergic diseases, and may be suitable for AERD patients [69,184]. Table 9 summarizes several drugs under investigation in controlled clinical trials, for the treatment of AERD and/or related pathologies.

Table 9
Medications under investigation in randomised controlled clinical trials for the treatment of AERD and/or related pathologies.

Medication name	Mechanism of action	Condition	Clinical trials identifier	Reference
Omalizumab	Blocks the binding of IgE to its high affinity receptor (FcεR1)	AERD	NCT00555971	[185]
Mepolizumab	Block the binding of IL-5 to its receptor expressed on the eosinophilic cell surface	Nasal polyps	NCT01362244, NCT03085797	[186,187]
Dupilumab	Antagonizes the IL-4α receptor, blocking IL-4 and IL-13 signaling	Nasal polyps and chronic symptoms of sinusitis	NCT02912468, NCT01920893	[188,189]
Lebrikizumab, tralokinumab, and GSK679586	Block the binding of IL-13 to its receptor	Severe oral corticosteroids dependent asthma. Asthma inadequately controlled on corticosteroids	NCT01987492, NCT02449473, NCT00843193	[190–192]
Brodalumab	Block IL-17 receptor A, inhibiting the biological activity of IL-17A, IL-17F and other IL-17 isoforms	Inadequately controlled asthma	NCT01902290	[193]
Prasugrel	Inhibits platelet activation and aggregation blocking p2Y12 receptor	AERD	NCT01597375	[194]
Ifetroban	Thromboxane A2/prostaglandin H2 receptor antagonist	AERD	NCT03326063, NCT02216357, NCT03028350	[195–197]
ARRY-502, AZD1981, Fevipiprant (QAW039), OC000459	CRTH2 antagonists, blocking PGD2 inflammatory effects	Persistent and severe asthma. Inadequately controlled asthma	NCT01561690, NCT00758589, NCT02555683, NCT02560610	[198–201]
GSK2190915	Inhibits 5-lipoxygenase activating protein	Moderate to severe asthma	NCT00850642	[202]

CRTH2, chemoattractant receptor homologous molecule expressed by Th2 lymphocytes.

8. Conclusions

Despite recent advances in the knowledge of the disease, AERD remains as a chronic and severe disease with refractory symptoms. The presence of pansinusitis, with sinonasal polyps, asthma, and intolerance to NSAIDs/salicylate rich food should suggest the diagnosis of AERD. Due to the severity of the symptoms, a prompt diagnosis is important to improve the patient's quality of life, and avoid, at least in part, complications like pulmonary fibrosis, hospitalizations due to ASA/NSAIDs ingestion, or even death.

The complexity of the disease is reflected in the interaction of several cells (eosinophils, mast cells, basophils, lymphocytes, platelets, neutrophils, macrophages, epithelial cells), and molecules, which results in an imbalance between pro-inflammatory and anti-inflammatory substances, expressed as an overproduction of CysLTs and an underproduction of PGE2.

Every cellular, molecular or genetic alteration found to be part of the pathogenesis of the disease is a potential diagnosis or treatment target. Although not specifically designed for the treatment of AERD, given their mechanism of action, drugs like omalizumab, anti-IL-5 monoclonal antibodies (mepolizumab, reslizumab, benralizumab), IL-4α receptor antagonist (dupilumab), anti-TSLP, thromboxane receptor antagonist (ifetroban), and PGD2 (CRTH2) antagonists are promissory therapeutic options. As a non-expensive therapeutic option, the low salicylate diet should be considered at least, in highly sensitive patients.

There is still much to be known about AERD, further research is strongly advised to improve the diagnostic tools and therapeutic options to help patients overcome the burden of the disease.

Competing interests

The authors declare that they have no competing interests.

Conflicts of interest

None

References

- [1] F. Widal, P. Abrami, J. Lermoyez, Anaphylaxie et Idiosyncrasie, Presse Med. 30 (1922) 189–193, <http://dx.doi.org/10.3109/02770908709070945>.
- [2] M. Samter, R.F. Beers, Intolerance to aspirin clinical studies and consideration of its pathogenesis, Ann. Intern. Med. 68 (1968).
- [3] L. Borris, Sinusitis and asthma: entering the realm of evidence-based medicine, J. Allergy Clin. Immunol. 109 (2002) 606–608, <http://dx.doi.org/10.1067/mai.2002.123024>.
- [4] J.M. Fahrenholz, Natural history and clinical features of aspirin-exacerbated respiratory disease, Clin. Rev. Allergy Immunol. 24 (2003) 113–124, <http://dx.doi.org/10.1385/CRIAI:24:2:113>.
- [5] A. Szczeklik, Mechanism of aspirin-induced asthma, Allergy 52 (1997) 613–619, <http://dx.doi.org/10.1111/j.1398-9995.1997.tb01039.x>.
- [6] J.W. Steinke, J.M. Wilson, Aspirin-exacerbated respiratory disease: pathophysiological insights and clinical advances, J. Asthma Allergy 9 (2016) 37–43, <http://dx.doi.org/10.2147/JAA.S88739>.
- [7] R.A. Simon, K.M. Dazy, J.D. Waldram, Aspirin-exacerbated respiratory disease: characteristics and management strategies, Expert Rev. Clin. Immunol. 11 (2015) 805–817, <http://dx.doi.org/10.1586/1744666X.2015.1039940>.
- [8] D.D. Stevenson, A. Szczeklik, Clinical and pathologic perspectives on aspirin sensitivity and asthma, J. Allergy Clin. Immunol. 118 (2006) 773–786, <http://dx.doi.org/10.1016/j.jaci.2006.07.024>.
- [9] M.P. Berges-Gimeno, R.A. Simon, D.D. Stevenson, The natural history and clinical characteristics of aspirin-exacerbated respiratory disease, Ann. Allergy Asthma Immunol. 89 (2002) 474–478, [http://dx.doi.org/10.1016/S1081-1206\(10\)62084-4](http://dx.doi.org/10.1016/S1081-1206(10)62084-4).
- [10] D.D. Stevenson, M. Sanchez-Borges, A. Szczeklik, Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes, Aai 87 (2001) 177–180, [http://dx.doi.org/10.1016/S1081-1206\(10\)62221-1](http://dx.doi.org/10.1016/S1081-1206(10)62221-1).
- [11] H. Rizk, Role of aspirin desensitization in the management of chronic rhinosinusitis, Curr. Opin. Otolaryngol. Head Neck Surg. 19 (2011) 210–217, <http://dx.doi.org/10.1097/MOO.0b013e3283450102>.
- [12] T.M. Laidlaw, J.A. Boyce, Aspirin-exacerbated respiratory disease — new prime suspects, N. Engl. J. Med. (2016) 484–488, <http://dx.doi.org/10.1056/NEJMcibr1514013>.
- [13] a Szczeklik, E. Nizankowska, M. Duplaga, Natural history of aspirin-induced

- asthma. AIAE investigators. European network on aspirin-induced asthma, *Eur. Respir. J. Off. J. Eur. Soc. Clin. Respir. Physiol* 16 (2000) 432–436, [http://dx.doi.org/10.1016/S1081-1206\(10\)62084-4](http://dx.doi.org/10.1016/S1081-1206(10)62084-4).
- [14] M.L. Kowalski, J.S. Makowska, Seven steps to the diagnosis of NSAIDs hypersensitivity: how to apply a new classification in real practice? *Allergy, Asthma Immunol. Res.* 7 (2015) 312–320, <http://dx.doi.org/10.4168/aaair.2015.7.4.312>.
 - [15] J.W. Steinke, L. Borish, Factors driving the aspirin exacerbated respiratory disease phenotype, *Am. J. Rhinol. Allergy* 29 (2015) 35–40, <http://dx.doi.org/10.2500/ajra.2015.29.4123>.
 - [16] J.-H. Choi, J.-H. Kim, H.-S. Park, Upper airways in aspirin-exacerbated respiratory disease, *Curr. Opin. Allergy Clin. Immunol.* 15 (2015) 21–26, <http://dx.doi.org/10.1097/ACI.0000000000000122>.
 - [17] R.U. Lee, D.D. Stevenson, Aspirin-exacerbated respiratory disease: evaluation and management, *Allergy. Asthma Immunol. Res.* 3 (2011) 3–10, <http://dx.doi.org/10.4168/aaair.2011.3.1.3>.
 - [18] D.R. Morales, B. Guthrie, B.J. Lipworth, C. Jackson, P.T. Donnan, V.H. Santiago, NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity, *Allergy Eur. J. Allergy Clin. Immunol* 70 (2015) 828–835, <http://dx.doi.org/10.1111/all.12629>.
 - [19] H. Vally, M.L. Taylor, P.J. Thompson, The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients, *Thorax* 57 (2002) 569–574, <http://dx.doi.org/10.1136/thorax.57.7.569>.
 - [20] J.P. Rajan, N.E. Wineinger, D.D. Stevenson, A.A. White, Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature, *J. Allergy Clin. Immunol.* 135 (2015) 676–681, <http://dx.doi.org/10.1016/j.jaci.2014.08.020> e1.
 - [21] K.L. Tuttle, T.R.S. Ba, S.E. Henrickson, D. Morris, J.P. Abonia, J.M. Spergel, T.M. Laidlaw, Aspirin-exacerbated respiratory disease: not always “adult-onset”, *J. Allergy Clin. Immunol. Pract* 4 (2016) 756–758, <http://dx.doi.org/10.1016/j.jaip.2016.05.016>.
 - [22] A. Szczeklik, E. Nizankowska, Clinical features and diagnosis of aspirin induced asthma, *Thorax* 55 (Suppl 2) (2000) S42–S44, http://dx.doi.org/10.1136/thorax.55.suppl_2.S42.
 - [23] H. Graefe, C. Roebke, D. Schäfer, J.E. Meyer, Aspirin sensitivity and chronic rhinosinusitis with polyps: a fatal combination, *J. Allergy* 2012 (2012) 1–10, <http://dx.doi.org/10.1155/2012/817910>.
 - [24] J.W. Spies, F.C.P. Valera, D.L. Cordeiro, T.N. de Mendonça, M.G.J. Leite, E. Tamashiro, L.K. Arruda, W.T. Anselmo-Lima, The role of aspirin desensitization in patients with aspirin-exacerbated respiratory disease (AERD), *Braz. J. Otorhinolaryngol* 82 (2016) 263–268, <http://dx.doi.org/10.1016/j.bjorl.2015.04.010>.
 - [25] A. Narayanankutty, I. Palma-Lara, G. Pavón-Romero, G. Pérez-Rubio, Á. Camarena, L.M. Teran, R. Falfán-Valencia, Association of TRPM3 polymorphism (rs10780946) and aspirin-exacerbated respiratory disease (AERD), *Lung* 194 (2016) 273–279, <http://dx.doi.org/10.1007/s00408-016-9852-9>.
 - [26] N.S. Palikhe, S.H. Kim, B.Y. Cho, Y.M. Ye, G.Y. Hur, H.S. Park, Association of three sets of high-affinity IgE receptor (FcεRI) polymorphisms with aspirin-intolerant asthma, *Respir. Med.* 102 (2008) 1132–1139, <http://dx.doi.org/10.1016/j.rmed.2008.03.017>.
 - [27] D.D. Stevenson, A.A. White, Clinical characteristics of respiratory disease, *Immunol. Allergy Clin.* (2016), <http://dx.doi.org/10.1016/j.iac.2016.06.002>.
 - [28] J.E. Chang, D. Ding, J. Martin-lazaro, A. White, D.D. Stevenson, Smoking, environmental tobacco smoke, and aspirin-exacerbated respiratory disease, *ANAI* 108 (2012) 14–19, <http://dx.doi.org/10.1016/j.anai.2011.09.022>.
 - [29] D.D. Stevenson, Aspirin sensitivity and desensitization for asthma and sinusitis, *Curr. Allergy Asthma Rep.* 9 (2009) 155–163, <http://dx.doi.org/10.1007/s11882-009-0023-4>.
 - [30] C.B. Johns, T.M. Laidlaw, Elevated total serum IgE in nonatopic patients with aspirin-exacerbated respiratory disease, *Am. J. Rhinol. Allergy* 28 (2014) 287–289, <http://dx.doi.org/10.2500/ajra.2014.28.4054>.
 - [31] A. Szczeklik, Aspirin-induced asthma as a viral disease, *Clin. Exp. Allergy* 18 (1988) 15–20, <http://dx.doi.org/10.1111/j.1365-2222.1988.tb02838.x>.
 - [32] W. Stevens, K. Buchheit, K.N. Cahill, Aspirin-exacerbated diseases: advances in asthma with nasal polyposis, urticaria, angioedema, and anaphylaxis, *Curr. Allergy Asthma Rep.* 15 (2015), <http://dx.doi.org/10.1007/s11882-015-0569-2>.
 - [33] J.R. Chen, B.L. Buchmiller, D.A. Khan, An hourly dose-escalation desensitization protocol for aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol. Pract* 3 (2015) 926–931, <http://dx.doi.org/10.1016/j.jaip.2015.06.013> e1.
 - [34] J. Makowska, A.L. Polak, M.L. Kowalski, Hypersensitivity to aspirin and other NSAIDs: diagnostic approach in patients with chronic rhinosinusitis, *curr. Allergy Asthma Rep* (2015), <http://dx.doi.org/10.1007/s11882-015-0552-y>.
 - [35] C. Jenkins, J. Costello, L. Hodge, Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice, *i* (n.d.) 1–7.
 - [36] G. Bochenek, K. Szafraniec, J. Kuschill-Dziurda, E. Nizankowska-Mogilnicka, Factors associated with asthma control in patients with aspirin-exacerbated respiratory disease, *Respir. Med.* 109 (2015) 588–595, <http://dx.doi.org/10.1016/j.rmed.2015.02.015>.
 - [37] D.D. Stevenson, Aspirin desensitization in patients with AERD, *Clin. Rev. Allergy Immunol.* 24 (2003) 159–168, <http://dx.doi.org/10.1385/CRIA:24:2:159>.
 - [38] K. Mascia, T. Haselkorn, Y.M. Deniz, D.P. Miller, E.R. Bleeker, L. Borish, Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma, *J. Allergy Clin. Immunol.* 116 (2005) 970–975, <http://dx.doi.org/10.1016/j.jaci.2005.08.035>.
 - [39] M.L. Kowalski, Rhinosinusitis and nasal polyposis in aspirin sensitive and aspirin tolerant patients: are they different? 84S–86, *Thorax* 55 (2000), http://dx.doi.org/10.1136/thorax.55.suppl_2.S84.
 - [40] J. Mullol, C. Picado, Rhinosinusitis and nasal polyps in aspirin-exacerbated respiratory disease, *Immunol. Allergy Clin.* 33 (2013) 163–176, <http://dx.doi.org/10.1016/j.iac.2012.11.002>.
 - [41] J. Young, S. Frenkiel, M.A. Tewfik, D.A. Mouadeb, Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis, *Am. J. Rhinol.* 21 (2007) 743–747, <http://dx.doi.org/10.2500/ajr.2007.21.3108>.
 - [42] K. Mascia, L. Borish, J. Patrie, J. Hunt, C.D. Phillips, J.W. Steinke, Chronic hyperplastic eosinophilic sinusitis as a predictor of aspirin-exacerbated respiratory disease, *Ann. Allergy Asthma Immunol.* 94 (2005) 652–657, [http://dx.doi.org/10.1016/S1081-1206\(10\)61323-3](http://dx.doi.org/10.1016/S1081-1206(10)61323-3).
 - [43] A. Szczeklik, M. Sanak, The broken balance in aspirin hypersensitivity, *Eur. J. Pharmacol.* 533 (2006) 145–155, <http://dx.doi.org/10.1016/j.ejphar.2005.12.053>.
 - [44] S.I. Vento, M.L. Hytonen, C.H. Wolff, C.H. Malmberg, Nasal polyposis: clinical course during 20 years, *Ann. Allergy Asthma Immunol.* 85 (2000) 209–214, [http://dx.doi.org/10.1016/S1081-1206\(10\)62468-4](http://dx.doi.org/10.1016/S1081-1206(10)62468-4).
 - [45] K.C. McMains, S.E. Kountakis, Medical and surgical considerations in patients with Samter's triad, *Am. J. Rhinol. Allergy* 20 (2006) 573–576, <http://dx.doi.org/10.2500/ajr.2006.20.2913>.
 - [46] W.W. Stevens, R.P. Schleimer, R.K. Chandra, A.T. Peters, Biology of nasal polyposis, *J. Allergy Clin. Immunol.* 133 (2014), <http://dx.doi.org/10.1016/j.jaci.2014.03.022> 1503–1503.e4.
 - [47] A. Majithia, T. Tatla, G. Sandhu, H.M. Saleh, P.M. Clarke, Intracranial polyps in patients with Samter's triad, *Am. J. Rhinol.* 21 (2007) 59–63, <http://dx.doi.org/10.2500/ajr.2007.21.2909>.
 - [48] J. Shen, M. Peterson, M. Mafee, Q.T. Nguyen, Aural Polyps in Samter's Triad: Case Report and Literature Review, (2012), pp. 774–778.
 - [49] B.J. Ferguson, B.A. Otto, H. Pant, When surgery, antibiotics, and steroids fail to resolve chronic rhinosinusitis, *Immunol. Allergy Clin.* 29 (2009) 719–732, <http://dx.doi.org/10.1016/j.iac.2009.07.009>.
 - [50] C. Picado, J. Castillo, J. Montserrat, A. Agusti-Vidal, Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation, *Eur. Respir. J.* 2 (1989) 127–129.
 - [51] N.H. Shah, T.R. Schneider, D. DeFaria Yeh, K.N. Cahill, T.M. Laidlaw, Eosinophilia-associated coronary artery vasospasm in patients with aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol. Pract* 4 (2016) 1215–1219, <http://dx.doi.org/10.1016/j.jaip.2016.04.028>.
 - [52] G. Bochenek, E. Nizankowska-Mogilnicka, Aspirin-Exacerbated Respiratory Disease as a Severe Clinical Disease and Diagnosis 33 (2013) 147–161, <http://dx.doi.org/10.1016/j.iac.2012.10.002>.
 - [53] R.A. Settiple, P.J. Schrank, R.A. Simon, D.A. Mathison, S.C. Christiansen, D.D. Stevenson, Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects, *J. Allergy Clin. Immunol.* 96 (1995) 480–485, [http://dx.doi.org/10.1016/S0091-6749\(95\)70290-3](http://dx.doi.org/10.1016/S0091-6749(95)70290-3).
 - [54] S. Bavbek, Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients: comparison of, 41 (2004) 67–75, <http://dx.doi.org/10.1081/JAS-120026063>.
 - [55] S. Bavbek, A. Berna, E. Dursun, Safety of Meloxicam in Aspirin-hypersensitive Patients with Asthma and/or Nasal Polyps, (2007), pp. 64–69, <http://dx.doi.org/10.1159/000096000>.
 - [56] A. Prieto, M. De Barrio, E. Martí, F.J. De Castro, F.J. Ruiz, Tolerability to Nabumetone and Meloxicam in Patients with Nonsteroidal Anti-inflammatory Drug Intolerance, (2007), pp. 960–964, <http://dx.doi.org/10.1016/j.jaci.2006.12.616>.
 - [57] F. Tepetam, B. Çolakoğlu, Tolerability of nimesulide in patients with histories of adverse reactions to acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, *Nobel Med* (2014) 81–87.
 - [58] C. Martín-García, M. Hinojosa, P. Berges, E. Camacho, R. García-Rodríguez, T. Alfaya, A. Iscar, Safety of a cyclooxygenase-2 inhibitor in patients with aspirin-sensitive asthma, *Chest* 121 (2002) 1812–1817, <http://dx.doi.org/10.1378/chest.121.6.1812>.
 - [59] Y. El Miedany, S. Youssef, I. Ahmed, M. El Gaafary, Safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-exacerbated respiratory disease, *Ann. Allergy Asthma Immunol.* 97 (2006) 105–109, [http://dx.doi.org/10.1016/S1081-1206\(10\)61378-6](http://dx.doi.org/10.1016/S1081-1206(10)61378-6).
 - [60] A. Valero, J. Sánchez-López, J. Bartra, C. Serrano, R. Muñoz-Cano, J. Roca, C. Picado, Safety of parecoxib in asthmatic patients with aspirin-exacerbated respiratory disease, *Int. Arch. Allergy Immunol.* 156 (2011) 221–223, <http://dx.doi.org/10.1159/000322841>.
 - [61] A. Szczeklik, E. Nizankowska, G. Bochenek, K. Nagraba, F. Mejza, M. Swierczyńska, Safety of a specific COX-2 inhibitor in aspirin-induced asthma, *Clin. Exp. Allergy* 31 (2001) 219–225, <http://dx.doi.org/10.1046/j.1365-2222.2001.01075.x>.
 - [62] D.D. Stevenson, R.A. Simon, Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma, *J. Allergy Clin. Immunol.* 108 (2001) 47–51, <http://dx.doi.org/10.1067/mai.2001.116290>.
 - [63] K.M. Woessner, R.A. Simon, D.D. Stevenson, The safety of celecoxib in patients with aspirin-sensitive asthma, *Arthritis Rheum.* 46 (2002) 2201–2206, <http://dx.doi.org/10.1002/art.10426>.
 - [64] P. Gyllfors, G. Bochenek, Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgesic drug celecoxib, *J. Allergy Clin. Immunol.* 111 (2003) 1116–1121.
 - [65] S. Baldassarre, L. Schandene, G. Choufani, A. Michils, Asthma attacks induced by low doses of celecoxib, aspirin, and acetaminophen, *J. Allergy Clin. Immunol.* 117 (2006) 215–217, <http://dx.doi.org/10.1016/j.jaci.2005.10.021>.
 - [66] J.C. Cardet, A.A. White, N.A. Barrett, A.M. Feldweg, P.G. Wickner, J. Savage,

- N. Bhattacharyya, T.M. Laidlaw, Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease, *e2*, *J. Allergy Clin. Immunol. Pract* 2 (2014) 208–213, <http://dx.doi.org/10.1016/j.jaip.2013.12.003>.
- [67] K.M. Woessner, Update on aspirin-exacerbated respiratory disease, *Curr. Allergy Asthma Rep.* 17 (2017) 2, <http://dx.doi.org/10.1007/s11882-017-0673-6>.
- [68] V. Ta, A.A. White, Survey-defined patient experiences with aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol. Pract* 3 (2015) 711–718, <http://dx.doi.org/10.1016/j.jaip.2015.03.001>.
- [69] K.M. Buchheit, T.M. Laidlaw, Update on the management of aspirin-exacerbated respiratory disease, *Allergy Asthma Immunol. Res.* 8 (2016) 298–304, <http://dx.doi.org/10.4168/air.2016.8.4.298>.
- [70] J. Chang, R.A. Simon, D.D. Stevenson, Aspirin-exacerbated respiratory disease: is it in our DNA? *Ann. Allergy, Asthma Immunol.* 106 (2011) 263–264, <http://dx.doi.org/10.1016/j.anai.2010.12.016>.
- [71] H.S. Cheong, S.M. Park, M.O. Kim, J.S. Park, J.Y. Lee, J.Y. Byun, B.L. Park, H.D. Shin, C.S. Park, Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics, *Allergy Eur. J. Allergy Clin. Immunol.* 66 (2011) 637–644, <http://dx.doi.org/10.1111/j.1398-9995.2010.02514.x>.
- [72] N.S. Palikhe, S.H. Kim, B.Y. Cho, Y.M. Ye, G.S. Choi, H.S. Park, Genetic variability in CRTH2 polymorphism increases eotaxin-2 levels in patients with aspirin exacerbated respiratory disease, *Allergy Eur. J. Allergy Clin. Immunol.* 65 (2010) 338–346, <http://dx.doi.org/10.1111/j.1398-9995.2009.02158.x>.
- [73] Y. Kanaoka, J.A. Boyce, Cysteinyl leukotrienes and their receptors; emerging concepts, *Allergy, Asthma Immunol. Res.* 6 (2014) 288–295, <http://dx.doi.org/10.4168/air.2014.6.4.288>.
- [74] T. Yoshimura, M. Yoshikawa, N. Otori, S. Haruna, H. Moriyama, Correlation between the prostaglandin D2/E2 ratio in nasal polyps and the recalcitrant pathophysiology of chronic rhinosinusitis associated with bronchial asthma, *Allergol. Int.* 57 (2008) 429–436, <http://dx.doi.org/10.2332/allergolint.0-08-545>.
- [75] A.S. Cowburn, K. Sladek, J. Soja, L. Adamek, E. Nizankowska, A. Szczeklik, B.K. Lam, J.F. Penrose, K.F. Austen, S.T. Holgate, A.P. Sampson, Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma, *J. Clin. Invest.* 101 (1998) 834–846, <http://dx.doi.org/10.1172/JCI620>.
- [76] C.A. Pérez-Novo, J.B. Watelet, C. Claeys, P. Van Cauwenberge, C. Bachert, Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis, *J. Allergy Clin. Immunol.* 115 (2005) 1189–1196, <http://dx.doi.org/10.1016/j.jaci.2005.02.029>.
- [77] J. Roca-Ferrer, F.J. Garcia-Garcia, J. Pereda, M. Perez-Gonzalez, L. Pujols, I. Alobid, J. Mullol, C. Picado, Reduced expression of COXs and production of prostaglandin E2 in patients with nasal polyps with or without aspirin-intolerant asthma, *J. Allergy Clin. Immunol.* 128 (2011) 66–72, <http://dx.doi.org/10.1016/j.jaci.2011.01.065>.
- [78] A.M. Adamusiak, O. Stasikowska-Kanicka, A. Lewandowska-Polak, M. Danilewicz, M. Wagrowska-Danilewicz, A. Jankowski, M.L. Kowalski, R. Pawliczak, Expression of arachidonate metabolism enzymes and receptors in nasal polyps of aspirin-hypersensitive asthmatics, *Int. Arch. Allergy Immunol.* 157 (2012) 354–362, <http://dx.doi.org/10.1159/000329744>.
- [79] T. Liu, T.M. Laidlaw, H.R. Katz, J. A. Boyce, Prostaglandin E2 deficiency causes a phenotype of aspirin sensitivity that depends on platelets and cysteinyl leukotrienes, *Proc. Natl. Acad. Sci. U. S. A.* 110 (2013) 16987–16992, <http://dx.doi.org/10.1073/pnas.1313185110>.
- [80] J.W. Steinke, D. Bradley, P. Arango, C.D. Crouse, H. Frierson, S.E. Kountakis, M. Kraft, L. Borish, Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma, *J. Allergy Clin. Immunol.* 111 (2003) 342–349, <http://dx.doi.org/10.1067/mai.2003.67>.
- [81] T.M. Laidlaw, J.A. Boyce, Platelets in aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 135 (2016) 1407–1415, <http://dx.doi.org/10.1016/j.jaci.2015.02.005>.
- [82] S.C. Payne, S.B. Early, P. Huyett, J.K. Han, L. Borish, J.W. Steinke, Evidence for distinct histologic profile of nasal polyps with and without eosinophilia, *Laryngoscope* 121 (2011) 2262–2267, <http://dx.doi.org/10.1002/lary.21969>.
- [83] E.M. Varga, M.R. Jacobson, K. Masuyama, S. Rak, S.J. Till, Y. Darby, Q. Hamid, V. Lund, G.K. Scadding, S.R. Durham, Inflammatory cell populations and cytokine mRNA expression in the nasal mucosa in aspirin-sensitive rhinitis, *Eur. Respir. J.* 14 (1999) 610–615, <http://www.ncbi.nlm.nih.gov/pubmed/10543283>.
- [84] C. Bachert, D. Ph. P. Gevaert, G. Holtappels, C. Cuvelier, D. Ph. P. Van Cauwenberge, D. Ph. Nasal Polyposis: from Cytokines to Growth, (2015), pp. 279–290.
- [85] G.S. Choi, J.H. Kim, Y.S. Shin, Y.M. Ye, S.H. Kim, H.S. Park, Eosinophil activation and novel mediators in the aspirin-induced nasal response in AERD, *Clin. Exp. Allergy* 43 (2013) 730–740, <http://dx.doi.org/10.1111/cea.12096>.
- [86] J.W. Steinke, J. Negri, L. Liu, S.C. Payne, L. Borish, Aspirin activation of eosinophils and mast cells: implications in the pathogenesis of aspirin-exacerbated respiratory disease, *J. Immunol.* 193 (2014) 41–47, <http://dx.doi.org/10.4049/jimmunol.1301753>.
- [87] T.M. Laidlaw, M.S. Kidder, N. Bhattacharyya, W. Xing, S. Shen, G.L. Milne, M.C. Castells, H. Chhay, J.A. Boyce, Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes, *Blood* 119 (2012) 3790–3798, <http://dx.doi.org/10.1182/blood-2011-10-384826>.
- [88] A. R. Fischer, M. A. Rosenberg, C.M. Lilly, J.C. Callery, P. Rubin, J. Cohn, M.V. White, Y. Igarashi, M. A. Kaliner, J.M. Drazen, Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma, *J. Allergy Clin. Immunol.* 94 (1994) 1046–1056, [http://dx.doi.org/10.1016/0091-6749\(94\)90123-6](http://dx.doi.org/10.1016/0091-6749(94)90123-6).
- [89] A. Narayanankutty, J.M. Reséndiz-Hernández, R. Falfán-Valencia, L.M. Teran, Biochemical pathogenesis of aspirin exacerbated respiratory disease (AERD), *Clin. Biochem.* 46 (2013) 566–578, <http://dx.doi.org/10.1016/j.clinbiochem.2012.12.005>.
- [90] T.C. Beller, D.S. Friend, A. Maekawa, B.K. Lam, K.F. Austen, Y. Kanaoka, Cysteinyl leukotriene 1 receptor controls the severity of chronic pulmonary inflammation and fibrosis, *Proc. Natl. Acad. Sci. U. S. A.* 101 (2004) 3047–3052, <http://dx.doi.org/10.1073/pnas.0400235101>.
- [91] C.I.N.A. Rhinosinusitis, Leukotriene-receptor expression on nasal mucosal inflammation, 347 (2002) 1493–1499.
- [92] C. Corrigan, K. Mallett, S. Ying, D. Roberts, A. Parikh, G. Scadding, T. Lee, Expression of the cysteinyl leukotriene receptors cysLT1 and cysLT2 in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis, *J. Allergy Clin. Immunol.* 115 (2005) 316–322, <http://dx.doi.org/10.1016/j.jaci.2004.10.051>.
- [93] S. Uematsu, M. Matsumoto, K. Takeda, S. Akira, Lipopolysaccharide-dependent prostaglandin E(2) production is regulated by the glutathione-dependent prostaglandin E(2) synthase gene induced by the Toll-like receptor 4/MyD88/NF-IL6 pathway, *J. Immunol.* 168 (2002) 5811–5816, <http://dx.doi.org/10.4049/jimmunol.168.11.5811>.
- [94] M. Murakami, K. Nakashima, D. Kamei, S. Masuda, Y. Ishikawa, T. Ishii, Y. Ohmura, K. Watanabe, I. Kudo, Cellular prostaglandin E2 production by membrane-bound prostaglandin E synthase-2 via both cyclooxygenases-1 and -2, *J. Biol. Chem.* 278 (2003) 37937–37947, <http://dx.doi.org/10.1074/jbc.M305108200>.
- [95] L. Machado-Carvalho, M. Martín, R. Torres, M. Gabasa, I. Alobid, J. Mullol, L. Pujols, J. Roca-Ferrer, C. Picado, Low E-prostanoid 2 receptor levels and deficient induction of the IL-1 β /IL-1 type I receptor/COX-2 pathway: vicious circle in patients with aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 137 (2016) 99–107, <http://dx.doi.org/10.1016/j.jaci.2015.09.028> e7.
- [96] S. Ying, Q. Meng, G. Scadding, A. Parikh, C.J. Corrigan, T.H. Lee, Aspirin-sensitive rhinosinusitis is associated with reduced E-prostanoid 2 receptor expression on nasal mucosal inflammatory cells, *J. Allergy Clin. Immunol.* 117 (2006) 312–318, <http://dx.doi.org/10.1016/j.jaci.2005.10.037>.
- [97] L. Machado-Carvalho, J. Roca-Ferrer, C. Picado, Prostaglandin E2 receptors in asthma and in chronic rhinosinusitis/nasal polyps with and without aspirin hypersensitivity, *Respir. Res.* 15 (2014) 100, <http://dx.doi.org/10.1186/s12931-014-0100-7>.
- [98] L.J. Kay, W.W. Yeo, P.T. Peachell, Prostaglandin E2 activates EP2 receptors to inhibit human lung mast cell degranulation, *Br. J. Pharmacol.* 147 (2006) 707–713, <http://dx.doi.org/10.1038/sj.bjp.0706664>.
- [99] J. Säfholm, M.L. Manson, J. Bood, I. Delin, A.C. Orre, P. Bergman, M. Al-Ameri, S.E. Dahlén, M. Adner, Prostaglandin E2 inhibits mast cell-dependent bronchoconstriction in human small airways through the E prostanoid subtype 2 receptor, *J. Allergy Clin. Immunol.* 136 (2015) 1232–1239, <http://dx.doi.org/10.1016/j.jaci.2015.04.002>.
- [100] N. Flamand, M.E. Surette, S. Picard, S. Bourgoin, P. Borgeat, Cyclic AMP-mediated inhibition of 5-lipoxygenase translocation and leukotriene biosynthesis in human neutrophils, *Mol. Pharmacol.* 62 (2002) 250–256, <http://dx.doi.org/10.1124/mol.62.2.250>.
- [101] G. Petrucci, R. De Cristofaro, S. Rutella, F.O. Ranalletti, D. Pocaterra, S. Lancellotti, A. Habib, C. Patrono, B. Rocca, Prostaglandin E2 differentially modulates human platelet function through the prostanoid EP2 and EP3 receptors, *J. Pharmacol. Exp. Therapeut.* 336 (2011) 391–402, <http://dx.doi.org/10.1124/jpet.110.174821>.
- [102] E.M. Sturm, P. Schratl, R. Schuligoi, V. Konya, G.J. Sturm, I.T. Lippe, B. A. Peskar, A. Heinemann, Prostaglandin E2 inhibits eosinophil trafficking through E-prostanoid 2 receptors, *J. Immunol.* 181 (2008) 7273–7283, <http://dx.doi.org/10.4049/jimmunol.181.10.7273>.
- [103] T.M. Laidlaw, A.J. Cutler, M.S. Kidder, Prostaglandin E2 resistance in granulocytes from patients with aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 133 (2014), <http://dx.doi.org/10.1016/j.jaci.2013.12.1034>.
- [104] C. Picado, J.C. Fernandez-Morata, M. Juan, J. Roca-Ferrer, M. Fuentes, A. Xaubet, J. Mullol, Cyclooxygenase-2 mRNA is down expressed in nasal polyps from aspirin-sensitive asthmatics, *Am. J. Respir. Crit. Care Med.* 160 (1999), <http://dx.doi.org/10.1164/ajrccm.160.1.9808048>.
- [105] T. Oguma, K. Asano, A. Ishizaka, Role of prostaglandin D(2) and its receptors in the pathophysiology of asthma, *Allergol. Int.* 57 (2008) 307–312, <http://dx.doi.org/10.2332/allergolint.08-RAI-0033>.
- [106] S.L. Johnston, N.J. Freezer, W. Ritter, S. O'Toole, P.H. Howarth, Prostaglandin D2-induced bronchoconstriction is mediated only in part by the thromboxane prostanoid receptor, *Eur. Respir. J.* 8 (1995) 411–415, <http://dx.doi.org/10.1183/09031936.95.08030411>.
- [107] K.M. Buchheit, K.N. Cahill, H.R. Katz, K.C. Murphy, C. Feng, K. Lee-Sarwar, J. Lai, N. Bhattacharyya, E. Israel, J.A. Boyce, T.M. Laidlaw, Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease, *e5*, *J. Allergy Clin. Immunol.* 137 (2016) 1566–1576, <http://dx.doi.org/10.1016/j.jaci.2015.10.020>.
- [108] K.N. Cahill, J.C. Bensko, J.A. Boyce, T.M. Laidlaw, Prostaglandin D2: a dominant mediator of aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 135 (2015) 245–252, <http://dx.doi.org/10.1016/j.jaci.2014.07.031>.
- [109] J.W. Steinke, L. Liu, P. Huyett, Prominent role of interferon- γ in aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 132 (2013), <http://dx.doi.org/10.1016/j.jaci.2013.05.008>.
- [110] R. Kennedy, D. Ph. Cytokine expression in peripheral blood lymphocytes before and after aspirin desensitization in aspirin-exacerbated respiratory disease, 28 (2007) 706–711, <http://dx.doi.org/10.2500/aap2007.28.3052>.
- [111] F.H. Hsieh, B.K. Lam, J.F. Penrose, K.F. Austen, J.A. Boyce, T helper cell type 2

- cytokines coordinately regulate immunoglobulin E-dependent cysteinyl leukotriene production by human cord blood-derived mast cells: profound induction of leukotriene C(4) synthase expression by interleukin 4, *J. Exp. Med.* 193 (2001) 123–133, <http://dx.doi.org/10.1084/jem.193.1.123>.
- [112] M. Thivierge, J. Stanková, M. Rola-Pleszczynski, IL-13 and IL-4 up-regulate cysteinyl leukotriene 1 receptor expression in human monocytes and macrophages, *J. Immunol.* 167 (2001) 2855–2860, <http://dx.doi.org/10.4049/jimmunol.167.5.2855>.
- [113] S.B. Early, E. Barekzi, J. Negri, K. Hise, L. Borish, J.W. Steinke, Concordant modulation of cysteinyl leukotriene receptor expression by IL-4 and IFN- γ on peripheral immune cells, *Am. J. Respir. Cell Mol. Biol.* 36 (2007) 715–720, <http://dx.doi.org/10.1165/rncmb.2006-0252OC>.
- [114] J.W. Steinke, J.A. Culp, E. Kropf, L. Borish, Modulation by aspirin of nuclear phospho-signal transducer and activator of transcription 6 expression: possible role in therapeutic benefit associated with aspirin desensitization, *J. Allergy Clin. Immunol.* 124 (2009) 724–730, <http://dx.doi.org/10.1016/j.jaci.2009.07.031> e4.
- [115] L.M. Teran, F. Ramirez-Jimenez, G. Soid-Raggi, J.R. Velazquez, Interleukin 16 and CCL17/thymus and activation-regulated chemokine in patients with aspirin-exacerbated respiratory disease, *Ann. Allergy Asthma Immunol.* 118 (2017) 191–196, <http://dx.doi.org/10.1016/j.anaai.2016.11.004>.
- [116] T. Liu, Y. Kanaoka, N.A. Barrett, Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway, *J. Immunol.* 195 (2015), <http://dx.doi.org/10.4049/jimmunol.1500905>.
- [117] G. Bochenek, K. Nagraba, E. Nizankowska, A. Szczeklik, A controlled study of 9 α ,11 β -PGF $_2$ (a prostaglandin D2 metabolite) in plasma and urine of patients with bronchial asthma and healthy controls after aspirin challenge, *J. Allergy Clin. Immunol.* 111 (2003) 743–749, <http://dx.doi.org/10.1067/mai.2003.1387>.
- [118] W.L. Song, J. Stubbe, E. Ricciotti, N. Alamuddin, S. Ibrahim, I. Crichton, M. Prempeh, J.A. Lawson, R.L. Wilensky, L.M. Rasmussen, E. Puré, G.A. FitzGerald, Niacin and biosynthesis of PGD $_2$ by platelet COX-1 in mice and humans, *J. Clin. Invest.* 122 (2012) 1459–1468, <http://dx.doi.org/10.1172/JCI59262>.
- [119] S.M. Park, J.S. Park, H.S. Park, C.S. Park, Unraveling the genetic basis of aspirin hypersensitivity in asthma beyond arachidonate pathways, *Allergy, Asthma Immunol. Res.* 5 (2013) 258–276, <http://dx.doi.org/10.4168/aaair.2013.5.5.258>.
- [120] J.H. Choi, K.W. Lee, H.B. Oh, K.J. Lee, Y.J. Suh, C.S. Park, H.S. Park, HLA association in aspirin-intolerant asthma: DPB1*0301 as a strong marker in a Korean population [3], *J. Allergy Clin. Immunol.* 113 (2004) 562–564, <http://dx.doi.org/10.1016/j.jaci.2003.12.012>.
- [121] S.W. Shin, J.S. Park, Y.J. Kim, T.J. Oh, S. An, C.S. Park, Differential gene expression profile in PBMCs from subjects with AERD and ATA: a gene marker for AERD, *Mol. Genet. Genom.* 287 (2012) 361–371, <http://dx.doi.org/10.1007/s00438-012-0685-9>.
- [122] A.B. Dursun, K.A. Woessner, R.A. Simon, D. Karasoy, D.D. Stevenson, Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis, *Ann. Allergy Asthma Immunol.* 100 (2008) 420–425, [http://dx.doi.org/10.1016/S1081-1206\(10\)60465-6](http://dx.doi.org/10.1016/S1081-1206(10)60465-6).
- [123] S. Donald, A. Ronald, Sensitivity to aspirin a non steroidal antiinflammatory drugs, *Allergy Princ. Pract.* 1998, pp. 1058–1066.
- [124] N.S. Palikhe, J.-H. Kim, H.-S. Park, Update on recent advances in the management of aspirin exacerbated respiratory disease, *Yonsei Med. J.* 50 (2009) 744–750, <http://dx.doi.org/10.3349/ymj.2009.50.6.744>.
- [125] Nizankowska-Mogilnicka, L. Bochenek, Mastalerz, EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity, 2 (2007) 1111–1118, <http://dx.doi.org/10.1111/j.1398-9995.2007.01409.x>.
- [126] J.L. Kennedy, A.N. Stoner, L. Borish, Aspirin-exacerbated respiratory disease: prevalence, diagnosis, treatment, and considerations for the future, *Am. J. Rhinol. Allergy* 30 (2016) 407–413, <http://dx.doi.org/10.2500/ajra.2016.30.4370>.
- [127] A.P. Hope, K.A. Woessner, R.A. Simon, D.D. Stevenson, Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 123 (2009) 406–410, <http://dx.doi.org/10.1016/j.jaci.2008.09.048>.
- [128] M. Milewski, L. Mastalerz, E. Nizankowska, A. Szczeklik, Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma, *J. Allergy Clin. Immunol.* 101 (1998) 581–586, [http://dx.doi.org/10.1016/S0091-6749\(98\)70163-0](http://dx.doi.org/10.1016/S0091-6749(98)70163-0).
- [129] A.A. White, J.V. Bosso, D.D. Stevenson, The clinical dilemma of “silent desensitization” in aspirin-exacerbated respiratory disease, *Allergy Asthma Proc.* 34 (2013) 378–382, <http://dx.doi.org/10.2500/aap.2013.34.3670>.
- [130] C. Jenneke, U. Juergens, M. Buecheler, N. Novak, Pathogenesis, diagnosis, and treatment of aspirin, 99 (2007) 13–21.
- [131] J. Casadevall, P.J. Ventura, J. Mullol, C. Picado, Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry, *Thorax* 55 (2000) 921–924, <http://dx.doi.org/10.1136/thorax.55.11.921>.
- [132] A. Alonso-Llamazares, C. Martinez-Cocera, J. Dominguez-Ortega, T. Robledo-Echarren, M. Cimarra-Alvarez, M. Mesa del Castillo, Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA), *Allergy* 57 (2002) 632–635 1s3447.
- [133] G. Scadding, Current Management of Aspirin-Exacerbated Respiratory Disease, (2012).
- [134] M.L. Sanz, P. Gamboa, A.L. De Weck, A new combined test with flowcytometric basophil activation and determination of sulfidoleukotrienes is useful for in vitro diagnosis of hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs, *Int. Arch. Allergy Immunol.* 136 (2005) 58–72, <http://dx.doi.org/10.1159/000082586>.
- [135] M.S. Kim, Y.J. Cho, Flow cytometry-assisted basophil activation test as a safe diagnostic tool for aspirin/NSAID hypersensitivity, *Allergy, Asthma Immunol. Res.* 4 (2012) 137–142, <http://dx.doi.org/10.4168/aaair.2012.4.3.137>.
- [136] M.L. Kowalski, A. Ptasińska, M. Jedrzejczak, B. Bienkiewicz, M. Cieslak, J. Grzegorzczak, R. Pawliczak, L. DuBuske, Aspirin-triggered 15-HETE generation in peripheral blood leukocytes is a specific and sensitive aspirin-sensitive patients identification test (ASPIrTest), *Allergy Eur. J. Allergy Clin. Immunol.* 60 (2005) 1139–1145, <http://dx.doi.org/10.1111/j.1398-9995.2005.00836.x>.
- [137] M.L. Kowalski, R. Pawliczak, J. Wozniak, K. Siuda, M. Poniatowska, J. Iwaszkiewicz, T. Kornatowski, M.A. Kaliner, Differential Metabolism of Arachidonic Acid in Nasal Polyp Epithelial Cells Cultured from Aspirin-sensitive and Aspirin-tolerant Patients, (n.d.).
- [138] B. Lebel, D. Messaad, V. Kvedariene, M. Rongier, J. Bousquet, P. Demoly, Cysteinyl-leukotriene release test (CAST) in the diagnosis of immediate drug reactions, *Allergy* 56 (2001) 688–692, <http://dx.doi.org/10.1034/j.1398-9995.2001.00103.x>.
- [139] E. Jerschow, Z. Ren, G. Hudes, M. Sanak, E. Morales, V. Schuster, S.D. Spivack, D. Rosenstreich, Utility of low-dose oral aspirin challenges for diagnosis of aspirin-exacerbated respiratory disease, *Ann. Allergy Asthma Immunol.* 116 (2016) 321–328, <http://dx.doi.org/10.1016/j.anaai.2015.12.026>.
- [140] J.B. Hagan, T.M. Laidlaw, R. Divekar, E.K. O'Brien, H. Kita, G.W. Volcheck, C.R. Hagan, D. Lal, H.G. Teaford, P.J. Erwin, N. Zhang, M.A. Rank, Urinary leukotriene E4 to determine aspirin intolerance in asthma: a systematic review and meta-analysis, *J. Allergy Clin. Immunol. Pract.* 5 (2017) 990–997, <http://dx.doi.org/10.1016/j.jaip.2016.11.004>.
- [141] L. Mastalerz, N. Celejewska-Wójcik, K. Wójcik, A. Gielicz, R. Januszek, A. Cholewa, P. Stręk, M. Sanak, Induced sputum eicosanoids during aspirin bronchial challenge of asthmatic patients with aspirin hypersensitivity, *Allergy Eur. J. Allergy Clin. Immunol.* 69 (2014) 1550–1559, <http://dx.doi.org/10.1111/all.12512>.
- [142] M. Sanak, A. Gielicz, G. Bochenek, M. Kaszuba, E. Niankowska-Mogilnicka, A. Szczeklik, Targeted eicosanoid lipidomics of exhaled breath condensate provide a distinct pattern in the aspirin-intolerant asthma phenotype, *J. Allergy Clin. Immunol.* 127 (2011) 1141–1147, <http://dx.doi.org/10.1016/j.jaci.2010.12.1108>.
- [143] W.W. Stevens, C.J. Ocampo, S. Berdnikovs, M. Sakashita, M. Mahdavinia, L. Suh, T. Takabayashi, J.E. Norton, K.E. Hulse, D.B. Conley, R.K. Chandra, B.K. Tan, A.T. Peters, L.C. Grammer, A. Kato, K.E. Harris, R.G. Carter, S. Fujieda, R.C. Kern, R.P. Schleimer, Cytokines in chronic rhinosinusitis role in eosinophilia and aspirin-exacerbated respiratory disease, *Am. J. Respir. Crit. Care Med.* 192 (2015) 682–694, <http://dx.doi.org/10.1164/rccm.201412-2278OC>.
- [144] H.K.T. Trinh, S.-C. Kim, K. Cho, S.-J. Kim, G.-Y. Ban, H.-J. Yoo, J.-Y. Cho, H.-S. Park, S.-H. Kim, Exploration of the sphingolipid metabolite, sphingosine-1-phosphate and sphingosine, as novel biomarkers for aspirin-exacerbated respiratory disease, *Sci. Rep.* 6 (2016) 36599, <http://dx.doi.org/10.1038/srep36599>.
- [145] Y.J. Suh, S.H. Yoon, A.P. Sampson, H.J. Kim, S.H. Kim, D.H. Nahm, C.H. Suh, H.S. Park, Specific immunoglobulin E for staphylococcal enterotoxins in nasal polyps from patients with aspirin-intolerant asthma, *Clin. Exp. Allergy* 34 (2004) 1270–1275, <http://dx.doi.org/10.1111/j.1365-2222.2004.02051.x>.
- [146] C.A. Pérez-Novo, M.L. Kowalski, P. Kuna, A. Ptasińska, G. Holtappels, P. Van Cauwenberge, P. Gevaert, S. Johansson, C. Bachert, Aspirin sensitivity and IgE antibodies to *Staphylococcus aureus* enterotoxins in nasal polyposis: studies on the relationship, *Int. Arch. Allergy Immunol.* 133 (2004) 255–260, <http://dx.doi.org/10.1159/000076832>.
- [147] D.D. Sommer, S. Hoffbauer, M. Au, L.J. Sowerby, M.K. Gupta, S. Nayan, Treatment of aspirin exacerbated respiratory disease with a low salicylate diet: a pilot crossover study, *Otolaryngol. Head Neck Surg.* 152 (2015) 42–47, <http://dx.doi.org/10.1177/0194599814555836>.
- [148] S. Nayan, A. Maby, B. Nutr, L.M. Endam, M. Desrosiers, Dietary modifications for refractory chronic rhinosinusitis? Manipulating diet for the modulation of inflammation, *Am. J. Rhinol. Allergy* 29 (2015) e170–e174, <http://dx.doi.org/10.2500/ajra.2015.29.4220>.
- [149] S. Doron, R. Brian, S. Leigh, A novel treatment adjunct for aspirin exacerbated respiratory disease: the low-salicylate diet: a multicenter randomized control crossover trial, 6 (2016) 385–391, <http://dx.doi.org/10.1002/alr.21678>.
- [150] A. Wood, G. Baxter, F. Thies, J. Kyle, G. Duthie, A systematic review of salicylates in foods: estimated daily intake of a Scottish population, *Mol. Nutr. Food Res.* 55 (2011) 7–14, <http://dx.doi.org/10.1002/mnfr.201000408>.
- [151] A.R. Swain, S.P. Dutton, A.S. Truswell, Salicylates in foods, *J. Am. Diet Assoc.* 85 (1985) 950–960.
- [152] High Omega-3/Low Omega-6 Treatment Diet for Aspirin-exacerbated Respiratory Disease (AERD). Available from: <https://clinicaltrials.gov/ct2/show/NCT02064738>. (Accessed 23 June 2017), (n.d.).
- [153] E. Healy, L. Newell, P. Howarth, P.S. Friedmann, Control of salicylate intolerance with fish oils, *Br. J. Dermatol.* 159 (2008) 1368–1369, <http://dx.doi.org/10.1111/j.1365-2133.2008.08830.x>.
- [154] N.D. Adappa, C.C. Wei, J.N. Palmer, Nasal irrigation with or without drugs: the evidence, *Curr. Opin. Otolaryngol. Head Neck Surg.* 20 (2012) 53–57, <http://dx.doi.org/10.1097/MOO.0b013e32834d8a80>.
- [155] L. Mastalerz, M. Milewski, M. Duplaga, E. Nizankowska, A. Szczeklik, Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma, *Allergy* 52 (1997) 895–900.
- [156] M.P. Berges-Gimeno, R.A. Simon, D.D. Stevenson, The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions, *Clin. Exp. Allergy* 32 (2002) 1491–1496, <http://dx.doi.org/10.1046/j.1365-2745.2002.01501.x>.

- [157] J.L. Wentzel, Z.M. Soler, K. DeYoung, S.A. Nguyen, S. Lohia, R.J. Schlosser, Leukotriene antagonists in nasal polyposis: a meta-analysis and systematic review, *Am. J. Rhinol. Allergy* 27 (2013) 482–489, <http://dx.doi.org/10.2500/ajra.2013.27.3976>.
- [158] S.E. Dahlén, K. Malmström, E.W.A. Nizankowska, B. Dahlén, P. Kuna, M. Kowalski, W.R. Lumry, C. Picado, D.D. Stevenson, J. Bousquet, R. Pauwels, S.T. Holgate, A. Shahane, J. Zhang, T.F. Reiss, A. Szczeklik, Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial, *Am. J. Respir. Crit. Care Med.* 165 (2002) 9–14, <http://dx.doi.org/10.1164/rccm.2010080>.
- [159] B. Dahlén, E. Nizankowska, A. Szczeklik, O. Zetterström, G. Bochenek, M. Kumlin, L. Mastalerz, G. Pinis, Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics, *Am. J. Respir. Crit. Care Med.* 157 (1998) 1187–1194, <http://dx.doi.org/10.1164/ajrccm.157.4.9707089>.
- [160] E.S. Walgama, P.H. Hwang, Aspirin-exacerbated respiratory disease, *Otolaryngol. Clin. 50* (2017) 83–94, <http://dx.doi.org/10.1016/j.otc.2016.08.007>.
- [161] S.A. Joe, R. Thambi, J. Huang, A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis, *Otolaryngol. Head Neck Surg.* 139 (2008) 340–347, <http://dx.doi.org/10.1016/j.otohns.2008.05.628>.
- [162] D.M. Poetker, Oral corticosteroids in the management of chronic rhinosinusitis with and without nasal polyps: risks and benefits, *Am. J. Rhinol. Allergy* 29 (2015) 339–342, <http://dx.doi.org/10.2500/ajra.2015.29.4223>.
- [163] K. Cho, E. Soudry, A. Psaltis, K. Nadeau, S. McGhee, J. Nayak, P. Hwang, Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease, *Otolaryngology-Head Neck Surg* 151 (2014) 575–581, <http://dx.doi.org/10.1177/0194599814545750>.
- [164] M.P. Berges-Gimeno, R.A. Simon, D.D. Stevenson, Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol.* 111 (2003) 180–186, <http://dx.doi.org/10.1067/mai.2003.7>.
- [165] J. Hill, T. Burnett, R. Katial, Mechanisms of benefit with aspirin therapy in aspirin-exacerbated respiratory disease, *Immunol. Allergy Clin.* 36 (2016) 735–747, <http://dx.doi.org/10.1016/j.iac.2016.06.011>.
- [166] M.P. Berges-Gimeno, S. Ronald, S. Donald, Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease, *Ann. Allergy Asthma Immunol.* 90 (2003) 338–341.
- [167] K.A. Cook, D.D. Stevenson, Current complications and treatment of aspirin-exacerbated respiratory disease, *Exp. Rev. Respir. Med.* 0 (2016) 1–12, <http://dx.doi.org/10.1080/17476348.2016.1258306>.
- [168] N.M. Dunn, R.K. Katial, Chronic rhinosinusitis and aspirin-exacerbated respiratory disease, *Immunol. Allergy Clin.* 36 (2016) 503–514, <http://dx.doi.org/10.1016/j.iac.2016.03.011>.
- [169] P.S. Batra, R.C. Kern, A. Tripathi, D.B. Conley, A.M. Ditto, G.K. Haines, P.R. Yarnold, L. Grammar, Outcome Analysis of Endoscopic Sinus Surgery in Patients with Nasal Polyps and Asthma, (2003), pp. 1703–1706.
- [170] O.G. Awad, J.H. Lee, M.B. Fasano, S.M. Graham, Sinonasal outcomes after endoscopic sinus surgery in asthmatic patients with nasal polyps: a difference between aspirin-tolerant and aspirin-induced asthma? *Laryngoscope* 118 (2008) 1282–1286, <http://dx.doi.org/10.1097/MLG.0b013e318170af1e>.
- [171] D. Mendelsohn, G. Jeremic, E.D. Wright, B.W. Rotenberg, Revision rates after endoscopic sinus surgery: a recurrence analysis, *Ann. Otol. Rhinol. Laryngol.* 120 (2011) 162–166, <http://dx.doi.org/10.1177/000348941112000304>.
- [172] K. Mc Mains, S. Kountakis, Medical and surgical considerations in patients with Samter's triad, *Am. J. Rhinol.* 20 (2006) 573–576.
- [173] A. White, E. Ludington, P. Mehra, D.D. Stevenson, R. a Simon, Effect of leukotriene modifier drugs on the safety of oral aspirin challenges, *Ann. Allergy Asthma Immunol.* 97 (2006) 688–693, [http://dx.doi.org/10.1016/S1081-1206\(10\)61101-5](http://dx.doi.org/10.1016/S1081-1206(10)61101-5).
- [174] E. Macy, J.A. Bernstein, M.C. Castells, S.M. Gawchik, T.H. Lee, R.A. Settipane, R.A. Simon, J. Wald, K.M. Woessner, A.D.J.T. Force, Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper, *Ann. Allergy Asthma Immunol.* 98 (2007) 172–174, [http://dx.doi.org/10.1016/S1081-1206\(10\)60692-8](http://dx.doi.org/10.1016/S1081-1206(10)60692-8).
- [175] J.Y. Lee, R.A. Simon, D.D. Stevenson, Selection of Aspirin Dosages for Aspirin Desensitization Treatment in Patients with Aspirin-exacerbated Respiratory Disease, (2003), pp. 157–164, <http://dx.doi.org/10.1016/j.jaci.2006.09.011>.
- [176] K.M. Woessner, A.A. White, Evidence-based approach to aspirin desensitization in aspirin-exacerbated respiratory disease, *e9, J. Allergy Clin. Immunol.* 133 (2014) 286–287, <http://dx.doi.org/10.1016/j.jaci.2013.11.016>.
- [177] I. Bobolea, P. Barranco, A. Fiandor, R. Cabañas, Omalizumab: a potential new therapeutic approach for aspirin-exacerbated respiratory disease, *J. Invest. Allergol. Clin. Immunol.* 20 (2010) 448–449.
- [178] E. Phillips-angles, P. Barranco, M. Lluch-bernal, J. Dominguez-ortega, V.L. Np, S. Quirce, Aspirin tolerance in patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease following treatment with omalizumab, *J. Allergy Clin. Immunol. Pract.* (n.d.) 1–4, doi:<http://dx.doi.org/10.1016/j.jaip.2016.12.013>.
- [179] B. Aerd, S.N. Hospital, T.E. Committee, S.N. Hospital, G. Evaluation, T. Effectiveness, Omalizumab reduces cysteinyl leukotriene and 9a,11b-prostaglandin F2 overproduction in aspirin-exacerbated respiratory disease, (n.d.), doi:<http://dx.doi.org/10.1016/j.jaci.2015.09.034>.
- [180] K.C. Bergmann, T. Zuberbier, M.K. Church, Omalizumab in the treatment of aspirin-exacerbated respiratory disease, *J. Allergy Clin. Immunol. Pract* 3 (2015) 459–460, <http://dx.doi.org/10.1016/j.jaip.2015.01.012>.
- [181] P. Gevaert, N. Van Bruaene, T. Cattaert, K. Van Steen, T. Van Zele, F. Acke, N. De Ruyc, K. Blomme, A.R. Sousa, R.P. Marshall, C. Bachert, Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis, *J. Allergy Clin. Immunol.* 128 (2011) 989–995, <http://dx.doi.org/10.1016/j.jaci.2011.07.056> e8.
- [182] S. Wenzel, L. Ford, D. Pearlman, S. Spector, L. Sher, F. Skobieranda, L. Wang, D. Ph, S. Kirkesseli, R. Rocklin, B. Bock, J. Hamilton, D. Ph, J.E. Ming, D. Ph, A. Radin, N. Stahl, D. Ph, G.D. Yancopoulos, D. Ph, N. Graham, G. Pirozzi, D. Ph, Dupilumab in Persistent Asthma with Elevated Eosinophil Levels, (2013), <http://dx.doi.org/10.1056/NEJMoa1304048>.
- [183] E.G. Sakalar, N.B. Muluk, M. Kar, C. Cingi, Aspirin-exacerbated respiratory disease and current treatment modalities, *Eur. Arch. Oto-Rhino-Laryngol.* (2016), <http://dx.doi.org/10.1007/s00405-016-4273-1>.
- [184] L. Uller, J.M. Mathiesen, L. Alenmyr, M. Korsgren, T. Ulven, T. Högborg, G. Andersson, C.G. Persson, E. Kostenis, Antagonism of the prostaglandin D2 receptor CRTH2 attenuates asthma pathology in mouse eosinophilic airway inflammation, *Respir. Res.* 8 (2007) 16, <http://dx.doi.org/10.1186/1465-9921-8-16>.
- [185] Therapeutic Utility of Xolair in Patients Undergoing Aspirin Desensitization. Available from: <https://clinicaltrials.gov/ct2/show/NCT00555971>. (Accessed 8 December 2017), (n.d.).
- [186] Effect of Mepolizumab in Severe Bilateral Nasal Polyps. Available from: <https://clinicaltrials.gov/ct2/show/NCT03085797>. (Accessed 8 December 2017), (n.d.).
- [187] Mepolizumab in Nasal Polyposis. Available from: <https://clinicaltrials.gov/ct2/show/NCT01362244>. (Accessed 8 December 2017), (n.d.).
- [188] An Evaluation of Dupilumab in Patients With Nasal Polyposis And Chronic Symptoms Of Sinusitis. Available from: <https://clinicaltrials.gov/ct2/show/NCT01920893>. (Accessed 8 December 2017), (n.d.).
- [189] A Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps (SINUS-24). Available from: <https://clinicaltrials.gov/ct2/show/NCT02912468>. (Accessed 8 December 2017), (n.d.).
- [190] Efficacy and Safety Study of GSK679586 in Patients With Severe Asthma. Available from: <https://clinicaltrials.gov/ct2/show/NCT00843193>. (Accessed 8 December 2017), (n.d.).
- [191] Study to Evaluate Efficacy & Safety of Tralokinumab in Subjects With Asthma Inadequately Controlled on Corticosteroids (MESOS). Available from: <https://clinicaltrials.gov/ct2/show/NCT02449473>. (Accessed 8 December 2017), (n.d.).
- [192] A Study of Lebrikizumab (RO5490255) in Participants With Severe Oral Corticosteroids (OCS) Dependent Asthma. Available from: <https://clinicaltrials.gov/ct2/show/NCT01987492>. (Accessed 8 December 2017), (n.d.).
- [193] Study of Efficacy and Safety of Brodalumab Compared With Placebo in Inadequately Controlled Asthma Subjects With High Bronchodilator Reversibility. Available from: <https://clinicaltrials.gov/ct2/show/NCT01902290>. (Accessed 8 December 2017), (n.d.).
- [194] Therapeutic Control of Aspirin-Exacerbated Respiratory Disease (Aspirin). Available from: <https://clinicaltrials.gov/ct2/show/NCT01597375>. (Accessed 8 December 2017), (n.d.).
- [195] Oral Ifetroban to Treat Aspirin Exacerbated Respiratory Disease (AERD). Available from: <https://clinicaltrials.gov/ct2/show/NCT03028350>. (Accessed 8 December 2017), (n.d.).
- [196] Trial to Determine the Safety of Oral Ifetroban in Patients With a History of Aspirin Exacerbated Respiratory Disease. Available from: <https://clinicaltrials.gov/ct2/show/NCT02216357>. (Accessed 8 December 2017), (n.d.).
- [197] Therapeutic Control of Aspirin-Exacerbated Respiratory Disease With Ifetroban. Available from: <https://clinicaltrials.gov/ct2/show/NCT03326063>. (Accessed 8 December 2017), (n.d.).
- [198] Effect of OC000459 on Eosinophilic Airway Inflammation in Severe Asthma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02560610>. (Accessed 8 December 2017), (n.d.).
- [199] Study of Efficacy and Safety of QAW039 in Patients With Severe Asthma Inadequately Controlled With Standard of Care Asthma Treatment. Available from: <https://clinicaltrials.gov/ct2/show/NCT02555683>. (Accessed 8 December 2017), (n.d.).
- [200] One Month Dose Response Study of AZD1981 in Asthma Patients Uncontrolled on Inhaled Steroids (OLIVE). Available from: <https://clinicaltrials.gov/ct2/show/NCT00758589>. (Accessed 8 December 2017), (n.d.).
- [201] A Study of ARRY-502 in Patients With Persistent Asthma. Available from: <https://clinicaltrials.gov/ct2/show/NCT01561690>. (Accessed 8 December 2017), (n.d.).
- [202] GSK2190915 Moderate to Severe Asthma Study. Available from: <https://clinicaltrials.gov/ct2/show/NCT00850642>. (Accessed 8 December 2017), (n.d.).