



NSAID-ERD Syndrome: the New Hope from Prevention, Early Diagnosis, and New Therapeutic Targets

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Abstract

Purpose of Review This review summarizes the latest information on the appropriate identification, evaluation, and treatment of patients with nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NSAID-ERD), also known as aspirin-exacerbated respiratory disease (AERD). Within the framework of our understanding of the underlying pathophysiology of NSAID-ERD, we also provide an update regarding new surgical techniques and newly available or upcoming medical therapies that may benefit these patients.

Recent Findings There have been considerable developments regarding recommendations for both the extent and timing of sinus surgery for NSAID-ERD. The last few years have also given us several new biologic medications that warrant consideration in the treatment of patients with recalcitrant NSAID-ERD. Further clinical trials are underway to investigate additional medications that may decrease the type 2 inflammation that dominates this disease.

Summary Despite the severe lower respiratory inflammation and recurrent nature of the nasal polyps in patients with NSAID-ERD, significant recent advances now afford much-improved quality of life for these patients. Careful collaboration between Allergy/Immunology and Rhinology specialists is imperative to ensure proper treatment of patients with NSAID-ERD.

Keywords AERD · NSAID-ERD · Nasal polyps · Asthma · Aspirin · NSAIDs

Introduction

NSAID-exacerbated respiratory disease (NSAID-ERD), also known as Aspirin-exacerbated respiratory disease (NSAID-ERD) or Samter's Triad, is a chronic inflammatory syndrome classically consisting of the triad of asthma, chronic rhinosinusitis with recurrent nasal polyps, and hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase-1 enzyme. This hypersensitivity manifests as respiratory reactions that occur

following ingestion or inhalation of NSAIDs. Systemic symptoms such as rash and gastrointestinal upset can also occur, although the exact cause of these reactions is not known. Although NSAID-induced respiratory reactions are a pathognomonic feature of the syndrome, the inflammatory respiratory disease begins and endures independently of NSAID exposure. However, the sudden onset of worsening symptoms that are observed in the setting of an NSAID-induced reaction serves as both the gold standard for the diagnosis of NSAID-ERD, and also offers insight into the pathophysiologic abnormalities that underlie the syndrome [1]. These insights are important to consider, as although NSAID-ERD is often categorized as a subset of asthma or of eosinophilic nasal polyposis, the entity is distinct enough to warrant more individualized therapies. To improve patient outcomes, further work is needed with both clinical efforts, as timely diagnosis of NSAID-ERD is required for patient safety and for the initiation of appropriate treatments, and research efforts, as the causative inflammatory mechanisms largely remain elusive [2], which has made the development of precision-targeted therapies nearly impossible.

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Symptoms, Evaluation, and Diagnosis

In general, NSAID-ERD develops quite suddenly in adulthood, usually in between the ages of 20 and 50 [3]. Patients present with asthma, often with onset in adulthood, nasal congestion, recurrent nasal polyps, and hyposmia or anosmia, and their symptoms are often not fully responsive to conventional therapies [3]. A characteristic feature of NSAID-ERD, and one that is required for the diagnosis, is that patients develop respiratory reactions to non-selective NSAIDs. These reactions typically involve both upper respiratory symptoms (increased nasal congestion, rhinorrhea, sinus pain, and sneezing) as well as lower respiratory symptoms (wheezing, shortness of breath, chest tightness, and fall in lung function), but they can also include a pruritic skin rash, abdominal pain, and occasionally vomiting [4].

An additional clinical finding is that about three quarters of all patients with NSAID-ERD report that they develop respiratory reactions after drinking alcohol. These reactions can cause symptoms in the upper or lower airways and are generally reported as being less severe than the NSAID-induced reactions. It does not appear to be specific to any particular type of alcohol and can occur after consuming less than one glass/drink [5, 6].

Unfortunately, there are no currently available and reliable in vitro tests that have been validated for the diagnosis of NSAID-ERD. Although systemic overproduction of leukotriene E₄ is the norm in NSAID-ERD, there are other diseases that can lead to leukotriene elevations, and the baseline levels are quite variable in patients with NSAID-ERD and do not provide sufficient sensitivity and specificity to warrant diagnostic utility [7]. Therefore, the diagnosis of NSAID-ERD remains a clinical one. For patients who present with a reliable history that includes all three of the cardinal triad of symptoms: asthma, nasal polyps, and respiratory reactions to NSAIDs, the diagnosis may sometimes be made on history alone. Asthma and nasal polyps are generally able to be confirmed through objective testing of pulmonary function and nasal endoscopic visualization. However, for patients in whom the possibility of reaction to an NSAID is not clear, it is important to do a formal aspirin challenge in order to confirm the diagnosis [8•, 9, 10]. This can be done either as an oral challenge, or as a combination of an intranasal and oral challenge, and the procedure should be done in a hospital or clinic with an experienced doctor and medical team. The patient is confirmed as reactive if they develop an aspirin-induced decrease in FEV₁ of $\geq 15\%$ from their baseline, and/or if they develop acute and objective worsening of nasal congestion, rhinorrhea, or ocular symptoms. Repeated assessment of patient-reported symptoms throughout the provocative challenge can help to quantify diagnostic findings [11].

From a sinus perspective, patients with NSAID-ERD tend to present with severe and quickly growing nasal polyps

associated with hyposmia. This inflammation is highly recalcitrant. Despite appropriate medical therapies and comprehensive sinus surgery, patients with NSAID-ERD have a higher incidence of polyp recurrence and history of multiple sinus surgeries compared to nasal polyp patients without aspirin sensitivity [12, 13•, 14].

Although not technically required as part of the diagnosis, mild-to-moderate peripheral eosinophilia is very common in NSAID-ERD [15], and striking nasal polyp tissue eosinophilia is the norm in surgical specimens examined from these patients [16]. Mast cells are also found within the nasal polyp tissue, and overall patients with NSAID-ERD tend to have slightly higher baseline serum tryptase levels than the healthy population, though these are rarely high enough levels to be considered out of the range of normal [17].

Epidemiology

Due to a lack of diagnostic in vitro assays and reliance on self-reported symptoms, a reliable estimate of the prevalence of NSAID-ERD in the general population is yet to be established [3]. However, a recent systematic review and meta-analysis of NSAID-ERD among patients with asthma identified 27 trials with important clinical insight [18•]. See Table 1 for a summary of NSAID-ERD prevalence among patients with asthma and nasal polyps.

In addition to the increased prevalence of NSAID-ERD among patients with more severe asthma, it is important to note limitations of patient-reported NSAID hypersensitivity as a predictive marker of NSAID-ERD. When evaluating the outcomes of diagnostic oral aspirin challenges among 243 patients with a clinical history concerning for NSAID-ERD, 42% (5 in 12) without a history of NSAID exposure had a positive reaction, while 14% (33 in 231) with a history of NSAID-associated asthma attacks failed to react during the formal challenge [19]. These limitations likely result in a significant population with unrecognized/undiagnosed NSAID-ERD. Underdiagnosis of NSAID-ERD was further established by Cahill et al., who utilized a regional health system database to define a computerized search strategy to identify patients with clinical criteria suspicious for NSAID-ERD (diagnosed asthma, nasal polyps, and NSAID hypersensitivity). Medical records from identified patients were then searched to confirm disease, revealing that > 12% of patients meeting clinical criteria for NSAID-ERD lacked the diagnosis

Table 1 Epidemiology of NSAID-ERD

1. Overall prevalence of 7.2% in patients with asthma.
2. Higher prevalence in patients with more severe lower airway disease, with prevalence of 14.9% in patients with severe asthma.
3. Prevalence of 9.7% in patients with asthma and chronic rhinosinusitis.

in their medical record and had not been referred for oral aspirin challenge or desensitization [20]. Despite concerns regarding the proper identification and diagnosis of NSAID-ERD, it is clear that this is not a rare disease. Based on a prevalence of 7.2% among the 19 million American patients with asthma, it is estimated that NSAID-ERD affects 1,368,000 patients in the USA alone [3].

Pathogenesis of Disease

The underlying causative mechanisms responsible for the pathogenesis of NSAID-ERD are not fully known. Dysregulation of the 5-lipoxygenase-leukotriene C₄ (LTC₄) synthase pathway, which converts arachidonic acid to the cysteinyl leukotrienes, is a hallmark of NSAID-ERD. Cysteinyl leukotrienes induce bronchoconstriction and mucous secretion, and also amplify eosinophilic inflammation. Levels of urinary leukotriene E₄ (LTE₄) from patients with NSAID-ERD exceed those from aspirin-tolerant controls, and they further increase during aspirin/NSAID-induced reactions [21]. These aspirin-induced elevations in LTE₄ are accompanied by increases in other products from activated mast cells, including tryptase and prostaglandin D₂ (PGD₂). It is thought that mast cell activation contributes substantially to both the clinical symptoms and the pathology seen during pathognomonic reactions [17]. For example, levels of PGD₂ are high in NSAID-ERD at baseline and also increase further during aspirin-induced reactions, especially in patients who develop the most severe systemic reactions [4]. PGD₂ can act through its CRTH2 receptor to induce activation and chemotaxis of eosinophils, basophils, and ILC2s, and in doing so is thought to lead to the acute recruitment of these cell types during aspirin-induced reactions, when PGD₂ is released in high quantities from the nasal tissue. Increased activation of both eosinophils and ILC2s, along with increased numbers of platelet-adherent granulocytes, may also play a role in the disease [16, 22, 23].

The exquisite dependence on COX-1 activity for the maintenance of homeostasis, which is thrown off balance after administration of any COX-1 inhibitor, may be due to abnormalities in the prostaglandin E₂ (PGE₂) pathway. PGE₂ is a COX product that acts as a key check to control 5-lipoxygenase activity and mast-cell activation. Fibroblasts in the nasal polyps of patients with NSAID-ERD may have an impaired ability to up-regulate the local production of PGE₂ [24]. Furthermore, PGE₂ signaling through its specific receptors also appears to be diminished in the cells of patients with NSAID-ERD as compared with that in controls, perhaps due to receptor downregulation [25, 26]. Without the availability of either sufficient PGE₂ production or adequate signaling capability, the respiratory tissue of patients with NSAID-ERD may be unable to maintain the needed “check” when

faced with further PGE₂ depletion secondary to pharmacologic inhibition of COX-1.

Recent evidence has suggested that the chronic eosinophilic respiratory inflammation that is the characteristic of NSAID-ERD may be related to the actions of interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP). These are innate cytokines derived from structural cells, and they can induce eosinophilic and Type 2 inflammation by acting directly on both lymphoid and myeloid effector cells, including mast cells [27]. Both IL-33 and TSLP are expressed strongly by nasal polyp tissue in NSAID-ERD, and nasal polyp TSLP messenger RNA expression correlates with the expression of mast cell markers, suggesting a potential mechanistic link [28, 29]. Using a mouse model of NSAID-ERD, we have found that blocking either IL-33 or its receptor completely prevents all of the aspirin-induced mast cell activation and subsequent changes in lung function [28]. With the advent of several new biologics aimed at either TSLP or the IL-33 signaling pathways, there is potential for the translation of these basic science studies into clinical trials of patients with NSAID-ERD.

Traditional/Standard Treatment and Management

Medical Management

It is important that patients with NSAID-ERD be educated to avoid aspirin and NSAIDs, but even with proper NSAID avoidance, the upper and lower respiratory symptoms are persistent. The mainstay of treatment for both the asthma and the sinus disease in NSAID-ERD is similar to that for aspirin-tolerant patients and includes inhaled steroids with or without a long-acting beta agonist, intranasal steroids, and use of systemic corticosteroids if needed. Leukotriene-modifying drugs are often a useful addition. Although montelukast, which blocks the cystLT1 receptor, is very commonly prescribed in NSAID-ERD, patients generally report that it is not nearly as efficacious as the less-commonly prescribed medication zileuton, which inhibits the 5-lipoxygenase enzyme, thereby decreasing production of cysteinyl leukotrienes [30]. Furthermore, zileuton is particularly effective at improving lung function patients with NSAID-ERD, likely due to their heightened sensitivity to the bronchoconstrictive effects of cysteinyl leukotrienes [31].

In addition to standard asthma and nasal polyp treatments, a protocol of aspirin desensitization to initiate daily high-dose aspirin therapy can be beneficial for many patients with NSAID-ERD. Desensitization to aspirin is achieved by giving increasing doses of aspirin until a reaction occurs and is treated – once the reaction abates, escalating doses are administered until the patient is able to take aspirin daily [8•, 9]. Daily aspirin therapy can reduce the rate of nasal polyp regrowth after surgery and can improve sense of smell and decrease the

need for systemic steroids, though the mechanism of action of daily aspirin is not yet clear [32–35]. A non-medical therapy that has been met with some success is dietary fatty acid modification with the goal to reduce consumption of omega-6 fatty acids, from which arachidonic acid, the precursor to cysteinyl leukotrienes, and PGD₂ is derived. One study showed that following a 2-week diet low in omega-6 and high in omega-3 fatty acids decreased urinary levels of LTE₄ and PGD₂ metabolites and improved nasal symptoms and asthma control in 10 patients with NSAID-ERD [36].

Surgical Management

Traditional sinus surgery for the management of NSAID-ERD follows the same guidelines and goals as for aspirin-tolerant patients with nasal polyps [37]. Goals of sinus surgery are several-fold and include both the surgical removal of obstructive polyps and pro-inflammatory eosinophilic secretions, as well as creating large openings into the affected sinuses to allow topical delivery of maintenance therapies, including saline and corticosteroids. The benefits of comprehensive sinus surgery extend well beyond improvement in sinonasal symptoms of nasal obstruction, rhinorrhea, facial pressure/pain, and smell dysfunction. In fact, a recent study showed improved levels of multiple mediators of upper and lower airway inflammation following sinus surgery, including decreased urinary LTE₄ and PGD₂ (detected as the urinary metabolite PGDM), as well as increased lipoxin A₄. These postoperative changes appear to be clinically significant as aspirin desensitization and initiation of high-dose aspirin therapy is more successful when performed following a recent sinus surgery in patients with previously challenge-confirmed NSAID-ERD [38–39].

Like for other forms of nasal polyps, sinus surgery in NSAID-ERD is only considered following the failure of what is considered “appropriate” medical management. This includes trials of nasal saline irrigation for ≥ 4 weeks, topical intranasal corticosteroid spray or irrigation for ≥ 8 weeks, and systemic corticosteroids for 1–3 weeks [40]. Only patients with recalcitrant sinonasal symptoms and objective evidence of upper airway inflammation (nasal endoscopy or computer tomography) that continued following use of appropriate medical therapies should be considered for surgery.

New/Emerging Therapies

New Surgical Therapies

Continuous innovation is a defining feature of sinus surgery and the field of otolaryngology in general. Advances in surgical technologies will allow for improved outcomes for a heterogeneous group of subjects with nasal polyps. However, appropriate indications and treatment outcomes for patients with NSAID-ERD remain to be clearly defined.

Multiple recent developments in technology and surgical approach support the emergence of the Endoscopic Modified Lothrop Procedure (EMLP), a frontal sinus “drill-out” first described in 1914 [41, 42]. This procedure effectively opens chronically obstructed frontal sinus ostia, a common nidus of recalcitrant inflammation and polyp recurrence. Increased penetration of sinonasal irrigations is noted following EMLP, resulting in a significantly lowered risk of revision sinus surgery among a heterogeneous population of patients with nasal polyps [43]. Among 229 patients with nasal polyps, 95% required no further surgical intervention at an average of 45 months following EMLP [44]. However, both comorbid asthma and NSAID-ERD are significant predictors of surgical failure. At an average of 36 months following EMLP for nasal polyps with NSAID-ERD, polyp recurrence was seen in 58% (18/31), with 22.5% (7/31) receiving revision surgery [45]. Despite advances in surgical method and technology, a multidisciplinary approach employing both surgery and innovative medical therapies is required for the long-term treatment of this recalcitrant disease.

Newly Available Medical Therapies

The past few years have given us several new biologic therapies for the treatment of severe and uncontrolled asthma, and/or CRSwNP, with further clinical trials for biologics and novel small molecules underway (Table 2). Although none of these are directed specifically for patients with NSAID-ERD, there are many scenarios where the application of one of these biologic therapies may be appropriate for and helpful to our patients with NSAID-ERD. The first new biologics to become available were anti-IL-5 or anti-IL-5Ra and are thought to be largely anti-eosinophil in their mechanism of action. As an add-on therapy for the severe and uncontrolled eosinophilic asthma that plagues many patients with NSAID-ERD, we have found mepolizumab, reslizumab, and benralizumab to be quite helpful [46–49]. There are also ongoing trials investigating the utility of anti-IL-5/Ra agents for the treatment of CRSwNP [50, 51], though in our anecdotal experience after using these medications for patients with NSAID-ERD, the therapeutic effects on the CRSwNP component of the disease have not been very dramatic. The other newly available biologic is dupilumab, an antibody that blocks the IL-4R α and therefore prevents signaling of both IL-4 and IL-13 through this common receptor. Dupilumab is now FDA-approved for both moderate to severe asthma and for CRSwNP [52–55], and the Phase 2 data for nasal polyposis suggests that it is particularly efficacious for patients with NSAID-ERD [56••]. Our clinical experience with using dupilumab for patients with NSAID-ERD has demonstrated good efficacy and relatively quick results so that patients will often notice a clear improvement in both their upper and lower respiratory symptoms within 2–4 weeks of starting dupilumab injections.

Table 2 New or upcoming therapies that may have therapeutic efficacy in NSAID-ERD

Target	Drug	Company	Indication	Phase
<i>Monoclonal antibodies</i>				
IL-5	Mepolizumab	GSK	CRSwNP	3
			Eosinophilic asthma	Approved
IL-5	Reslizumab	Teva	Eosinophilic asthma	Approved
IL-5R α	Benralizumab	AstraZeneca	CRSwNP	3
			Eosinophilic asthma	Approved
IL-4R α	Dupilumab	Sanofi / Regeneron	CRSwNP	Approved
			Eosinophilic asthma	Approved
IgE	Omalizumab	Hoffmann-La Roche / Genentech / Novartis	CRSwNP	3
			Allergic asthma	Approved
TSLP	Tezepelumab / AMG 157	AstraZeneca	Asthma	3
IL-33 or ST2	AMG 282	Amgen	CRSwNP	1
			Atopic asthma	1
	REGN3500	Sanofi-Genzyme & Regeneron	Asthma	1
	Etokimab / ANB020	AnaptysBio	CRSwNP	2
			Asthma	2
<i>Orally bioavailable medications</i>				
CRTH2 (DP2)	GB001	Gossamer Bio	CRSwNP & sNP	2
	ACT-774312	Idorsia	NP	2
	Fevipirant	Novartis	NP + asthma	3
Thromboxane receptor	Ifetroban	Cumberland	NSAID-ERD	2
Ca ⁺⁺ Channel	Verapamil	Generic	CRSwNP	1–2

CRSwNP – chronic rhinosinusitis with nasal polyposis; NP – nasal polyposis; NSAID-ERD – Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; CRTH2 – Chemoattractant receptor-homologous molecule expressed on T_H2 cells; DP2 – Prostaglandin D2 receptor 2

Potential Future Medical Targets

There are a number of exciting new studies underway for both severe asthma and for CRSwNP, several of which may hold particular promise for patients with NSAID-ERD (Table 2). As mentioned above, there is ample evidence from lab bench studies to suggest that TSLP and IL-33 may play a direct role in the maintenance of chronic respiratory inflammation and mast cell activation in NSAID-ERD and may also be implicated in the mechanism of aspirin-induced reactions. Both anti-TSLP and anti-IL-33 biologics are making their way through ongoing clinical trials for asthma and/or CRSwNP, and we are hopeful that the study results will be sufficiently positive to warrant approval [57, 58]. In addition, as the pro-inflammatory role of PGD₂ has now been clearly demonstrated in NSAID-ERD [4, 29], and many of the CRTH2⁺ effector cells (eosinophils, basophils, ILC2s, and mast cells) appear to be involved in the respiratory inflammation characteristic of NSAID-ERD; there is great potential for the upcoming orally bioavailable anti-CRTH2 medications to provide therapeutic benefit. These drugs could become part of the daily medical regimen of our patients, or perhaps could be used more selectively to prevent or abrogate the aspirin-induced reactions, as recruitment of CRTH2⁺ cells to the respiratory mucosa is a

hallmark of these reactions [23, 59]. Finally, the inflammatory role of platelets, perhaps largely through the activation of the thromboxane receptor, has been demonstrated in NSAID-ERD [22, 60, 61], and the investigation of ifetroban, a thromboxane receptor antagonist, shows promise as an additional NSAID-ERD-specific treatment.

Conclusion

NSAID-ERD is a severe inflammatory syndrome characterized by chronic upper and lower airway inflammation and severe impairment of quality of life for > 7% of all adult patients with asthma. Dysregulation of the 5-lipoxygenase–LTC₄ synthase pathway leaves patients critically dependent on COX-1 activity to maintain production of anti-inflammatory PGE₂. NSAID-induced COX-1 inhibition leads to further reduction of PGE₂ and the pathognomonic reactions characteristic of this disease.

Despite a progressive course with few options for disease-specific treatment, future care for NSAID-ERD is bright. Recently approved biologic medications target mediators specific for the type-2 inflammation driving this disease. Additionally, ongoing studies are posed to introduce further

treatment options, with biologic inhibitors of epithelial-derived cytokines (TSLP and IL-33) and orally available CRTH2 and thromboxane receptor antagonists representing novel therapeutic options.

Nasal polyp recurrence following surgery is higher among patients with NSAID-ERD compared to aspirin-tolerant patients with nasal polyps. However, sinus surgery remains an essential component of multidisciplinary care. Completion of comprehensive sinus surgery with wide opening of all sinuses is associated with increased penetration of topical corticosteroids, as well as decreased aspirin reactivity, likely secondary to improvement in systemic levels of several inflammatory mediators. To improve care for our patients with NSAID-ERD, we must continue to work collaboratively and clearly define appropriate indications for, and the sequence of, these emerging therapies.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Laidlaw reports personal fees from Regeneron, personal fees from Sanofi, personal fees from GlaxoSmithKline, outside the submitted work, Dr. Lev declares no conflicts of interest relevant to this manuscript.

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

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