

EXPERT
REVIEWS

Topical nasal lysine aspirin in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis with nasal polyposis

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Chronic rhinosinusitis patients with nasal polyps can be aspirin sensitive or aspirin tolerant. The majority belong to the latter group. They tolerate intake of aspirin or other non-steroidal anti-inflammatory drugs, whereas aspirin-sensitive patients have an adverse reaction (asthma, rhinitis and/or urticaria). Diagnosis of aspirin sensitivity is important for the patient, but is rarely undertaken in routine ENT or respiratory medicine practice. Treatment of nasal polyps is by a combination of medical therapy and surgery. Oral and topical steroids form the mainstay of medical therapy, which is aimed at reducing inflammation and symptom improvement. Surgery helps with polyps causing severe nasal obstruction. Despite these therapies, recurrences are common in aspirin sensitive patients. Any adjunctive therapy to prevent or prolong recurrence would be welcome. One such possibility is topical nasal lysine-aspirin. This is an area under current debate and this non-systematic review aims to provide evidence of its use, to date, in aspirin sensitive and aspirin tolerant nasal polyp patients.

KEYWORDS: aspirin sensitive • aspirin tolerant • desensitization • lysine-aspirin • nasal polyps

Chronic rhinosinusitis (CRS) with nasal polyposis causes symptomatic disease, which can be debilitating in some 2% of the population. The majority of polyps in European practice are characterized by eosinophilic inflammation and tend to recur following surgery, whether endoscopic or not. The speed of recurrence is proportional to the degree of inflammation with aspirin-sensitive polyps regrowing rapidly following surgery and/or systemic corticosteroids. Surgery and/or systemic corticosteroids can be repeated sometimes, but it is usual to attempt a delay in polyp growth by other therapies, most used topically in the nose, directly on to polyp tissue.

A recent review [1] of topical therapy noted that high-quality evidence supports the effectiveness of saline irrigations in treating CRS. There is insufficient evidence to support topical antibiotics, and topical antifungal therapies are not significantly different in efficacy from saline controls on CRS outcomes. Topical

steroids are beneficial in CRS with nasal polyps, but have not been shown to be effective in CRS without nasal polyps.

Notably absent from this review is the intranasal use of lysine aspirin in nasal polyposis.

Aspirin & aspirin sensitivity

Acetylsalicylic acid or aspirin has been marketed commercially since 1899 [2]. Anaphylaxis to aspirin was reported soon thereafter [3], but reaction to a small dose of the drug was first reported in 1911, under the heading 'idiosyncrasy' [4]. With the increasing awareness of these idiosyncratic reactions, physicians grouped together cases to present common clinical features. The association of aspirin idiosyncrasy, aspirin-induced asthma and nasal polyps was first published in 1922 [5]. Since then, several series have been published [6–8], but the first comprehensive study on a large group of patients was published in 1968. Commenting on the triad of aspirin-induced

Table 1. Types of adverse reaction to aspirin and nonsteroidal anti-inflammatory drugs.

Acute (within minutes to hours)		Delayed (>24 h)	
Allergic	Nonallergic	Allergic	Nonallergic
Urticaria Angioedema Anaphylaxis	Rhinitis Asthma Wheals Urticaria Angioedema	Fixed drug eruptions Exanthema Pneumonitis Nephritis Aseptic meningitis	Wheals Angioedema Urticaria
IgE mediated	Biochemical reaction due to COX-1 inhibition	T cell mediated	Biochemical reaction due to COX-1 inhibition
Reaction to specific drug (single agent)	Reaction to a group of drugs with similar chemical configuration (cross-reactive)	Reaction to specific drug (single agent)	Reaction to a group of drugs with similar chemical configuration (cross-reactive)

adverse reaction(s), asthma and nasal polyps, the authors reported that “it is a disease entity, not a chance cluster of allergic symptoms, and represents, in fact, the prototype of a syndrome that has not been previously described and deserves recognition” [9]. Thus, it has been suggested by many that this triad should be called Samter’s triad after the first author of that paper [10].

Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), was found to cause the same idiosyncratic reaction in aspirin-sensitive individuals [11]. Aspirin and NSAID(s) have similar pharmacological actions in inhibiting cyclooxygenase enzymes [12], and hence all drugs in this category can cause this reaction, with severity relating to the degree of COX-1 inhibition [13].

Although there are recommendations to call affected individuals NSAID hypersensitive rather than aspirin sensitive or aspirin intolerant [14], the terminology aspirin exacerbated respiratory disease (AERD) is frequently used, since it encapsulates the fact that the disease exists even if aspirin is avoided.

Reactions to aspirin & NSAIDs

Aspirin and other NSAIDs are responsible for 21–25% of reported adverse drug events. Several types of reactions to aspirin and NSAIDs are seen (TABLE 1) [9,14,15].

Respiratory reactions are the commonest seen in 85% of individuals who are aspirin sensitive [9]. The reaction starts typically after 20–30 min of taking aspirin/NSAID, but can start any time from 10 min to 2 h. The lower airway reaction leads to an attack of asthma that can be severe and unresponsive to conventional medication. Some individuals may need hospitalization and intensive care admission. Fatalities have been reported. The upper airway or nasal reaction includes symptoms of itching, sneezing, rhinorrhea and nasal blockage. An isolated nasal reaction is seen in a very small proportion of individuals. Most will have a combination of upper and lower respiratory reaction, but the lower airway reaction can be sufficiently intense to overshadow nasal symptoms.

Isolated skin and soft tissue reactions are seen in 10% of aspirin-sensitive individuals, manifesting as urticaria and/or angioedema. Unlike the respiratory reaction, it can occur up to 14 h after aspirin/NSAID intake. Facial swelling is seen

particularly around the eyes and lips. Occasionally, the edema is severe involving the tongue and larynx. This can be fatal.

The remaining 5% of aspirin-sensitive individuals have both the above-mentioned reactions.

Use of aspirin in aspirin-sensitive patients

For diagnosis

Direct intake of aspirin as in a challenge test remains the only conclusive method to prove if an individual is aspirin sensitive [16] since *in vitro* tests lack sufficient sensitivity and specificity. An oral challenge is considered to be the ‘gold standard’ method for diagnosis, with a sensitivity of 89% and a specificity of 93% [14,16]. Standardized protocols have been introduced and refined over the past four decades [14,16–19].

Lysine aspirin or lysine-acetylsalicylate (LAS) has a slightly different molecular structure to aspirin. It is a salt of aspirin made by attaching a lysine molecule to acetylsalicylic acid. Lysine, an amino acid, has no analgesic effect, but it allows the aspirin to be soluble in liquids. This characteristic of solubility makes it suitable for injections and topical use as in an inhalational or nasal challenge.

Inhalation challenge or bronchial provocation test using LAS was introduced in 1977 [20]. The method is safer and quicker than an oral challenge [16,19]. The challenge is considered to be positive if FEV₁ drops by 20%. Most reactions occur in 30–45 min. The sensitivity and specificity for this test are 77 and 93%, respectively [16].

Aspirin nasal challenge (TABLE 2) [16,21–25] was first used in 1987 to study the release of mediators [26] and these nasal lavage studies provided valuable insight into the mechanisms involved in aspirin sensitivity [27]. In 1989, aspirin in powder form was used unsuccessfully as a diagnostic aid [28]. The authors concluded that a nasal challenge test was not a useful diagnostic method. It was not until the soluble form, lysine aspirin, was used that positive results were obtained and its value as a safe test established [29]. The optimal dose to induce a positive reaction in aspirin-sensitive individuals was found to be 12 mg [30]. Since these early studies, aspirin nasal challenge has been evaluated in detail [22] and challenge protocols published [19]. It has also been shown to be an effective and safe diagnostic method

Table 2. Lysine aspirin as a diagnostic tool.

Study (year)	Type of challenge	Dose (aspirin equivalent mg)	Parameter measured	Results				Ref.
				Sen	Spec	PPV	NPV	
Schapowal <i>et al.</i> (1995)	Nasal	1.25	AR	93	97			[21]
Milewski <i>et al.</i> (1998)	Nasal	16	AR + Symptoms	78	95.6	96.9	71	[22]
Casadevall <i>et al.</i> (2000)	Nasal	25	AcR	94	73			[23]
Nizankowska <i>et al.</i> (2000)	Bronchial	0.18–182 (cum. dose)	PEFR + Symptoms	77	93	96	64	[16]
Barranco <i>et al.</i> (2009)	Bronchial	0.25–17.1 (cum. dose)	PEFR + FEV ₁	70	100	100	80	[24]
Miller <i>et al.</i> (2013)	Nasal	2.8–42 (cum. dose)	AcR + NIPF + Symptoms	88	100	100	55	[25]

AcR: Acoustic rhinometry; AR: Active anterior rhinomanometry; cum.: Cumulative dose; NIPF: Nasal inspiratory peak flow (litres/min); NPV: Negative predictive value; PEFR: Peak expiratory flow rate (litres/min); Sen: Sensitivity; Spec: Specificity; PPV: Positive predictive value.

used in a day case setting [25]. The sensitivity and specificity are reported as 86.7 and 95.6%, respectively [22].

A negative nasal lysine aspirin challenge is not definitive proof of the absence of aspirin sensitivity and needs to be followed by oral challenge. Usually, the whole can be completed in a 1 day outpatient or day care setting. Since highly sensitive subjects react early in the procedure to nasal doses, there is less likelihood of a severe reaction to oral aspirin [25].

A drawback is its inconsistency in patients with almost complete nasal obstruction or those that have large fluctuations in nasal airflow measurements. To circumvent these problems, patients with very obstructive polyps are treated either by oral plus nasal corticosteroids or by surgery prior to challenge, placebo used to exclude nonspecific hyper-reactivity and acoustic rhinometry, which is an instrument for accurately assessing upper airway dimensions, is employed [23,25].

For treatment

The 'refractory period'

In aspirin-sensitive individuals, there is a time phase after aspirin ingestion wherein repeat intake will not lead to an adverse reaction. This has been called the 'refractory period'. Although its existence was first recognized in 1922 [5], the phenomenon was accidentally rediscovered during diagnostic oral challenges [20] in which the patient underwent an oral challenge on five separate occasions and on each of these, there was a clear indication of a refractory period. This period lasted 72 h.

Such a refractory period has also been demonstrated in patients following bronchial provocation [20] and after nasal challenge [31]. Further confirmation of this period came from a study on two aspirin-sensitive patients, both could tolerate taking aspirin daily after an initial positive oral challenge [32]. The dose of aspirin was gradually increased to 1200 mg/day in one patient and 625 mg/day in the other without adverse effects.

Studies have shown that the length of this refractory period can vary between 1 and 9 days [33,34].

Desensitization

Investigators studying the refractory period in two aspirin-sensitive patients noticed that their clinical condition improved

significantly [32]. Within 6 months of daily aspirin use, their nasal symptoms resolved, FEV₁ increased and oral corticosteroid intake reduced. This phenomenon was called 'desensitization'. A further study on 30 aspirin-sensitive patients showed that they could all be desensitized by using incremental doses of oral aspirin [18].

Desensitization using oral aspirin

Since these initial observations, several short-term and long-term studies have been published, all showing the therapeutic benefits of oral aspirin desensitization [35–46]. Only one study in this group was a double-blind, placebo controlled trial [37].

Desensitization leads to a reduction in episodes of acute asthma, fall in number of asthma-related hospital admissions, decrease in steroid dependency, improvement in chest scores and pulmonary function [38,39,43,47]. It also improves nasal blockage, nasal discharge, sense of smell, sinonasal quality of life scores and reduces the need for repeated nasal polyp operations [38,41–43,45].

To sustain a patient in a desensitized state, the daily dose of oral aspirin has ranged from 100 to 2600 mg. At these doses, several studies have reported side effects, primarily gastrointestinal upset (14–20%), easy bruising and a tendency to 'escape' the desensitized state at low doses [36,37,43,48].

Desensitization using topical nasal aspirin (TABLE 3) [21,49–52]

The presence of a refractory period after nasal challenge [31] prompted the investigators to study the effects of topical LAS on nasal polyp growth [49]. They used a low dose of LAS (equivalent to 2 mg of aspirin), and polyp growth was measured using anterior rhinomanometry. Aspirin-sensitive patients (n = 28) receiving topical LAS were compared with a control group of 130 aspirin-sensitive patients who did not receive any topical treatment. Both groups were followed for 24 months with 3 monthly examinations and measurements. Patients on topical LAS did much better than the control group. Recurrence of nasal polyps was seen in 32% receiving topical LAS compared with 81% of aspirin-sensitive controls. More importantly, no patient with asthma noticed any deterioration and there were no systemic side effects.

Table 3. Nasal lysine aspirin in aspirin-sensitive nasal polyposis

Study (year)	Type of trial	Dose (aspirin equivalent mgs)	n	Period of study (months)	Outcome measures	Results	Ref.
Patriaca <i>et al.</i> (1991)	Prospective, with non randomized controls	2	28	24	Relapse of polyps	Relapse rate reduced in lysine aspirin group	[49]
Schapowal <i>et al.</i> (1995)	Randomised, double-blind, placebo controlled	55	12	1	Nasal symptoms (arbitrary scales 0–4) Nasal polyps Smell sense	No difference between lysine aspirin and placebo groups	[21]
Nucera <i>et al.</i> (2000)	Prospective, with controls	4	38	72	Recurrence of nasal polyps	Recurrence reduced in lysine aspirin group	[50]
Parikh and Scadding (2005)	Prospective, randomized, double-blind, placebo controlled, cross-over	16	11	12	Polyp growth Cys LTR1 numbers	No significant difference when patients were on lysine aspirin or placebo Reduction in cys LTR1	[51]
Ogata <i>et al.</i> (2007)	Prospective, open	37.8	13	6	Nasal polyp volume	Polyp volume reduction with lysine aspirin	[52]
Howe <i>et al.</i> ; In press	Audit	75–100	109	12	NIPF Olfaction Exhaled/nasal NO Asthma questionnaire	Improvement ($p < 0.05$) Improvement ($p < 0.05$) Improvement ($p < 0.05$) < emergency visits ($p = 0.0182$) < hospital admissions ($p = 0.0074$) < oral steroid need ($p = 0.004$)	[Pers. COMM.]

CysLTR1: Cysteinyl leukotriene receptor 1; NIPF: Nasal inspiratory peak flow (l/min); NO: Nitric oxide.

Two further studies showing long-term benefits were published in 2000 [50]. Aspirin-sensitive and aspirin-tolerant patients with nasal polyps were included. A group of 191 age-matched patients who did not have any medical treatment following previous surgical polypectomy served as controls. The first was a 6-year follow-up study on 76 polyp patients treated with surgery, and 1-month postsurgery started on intranasal LAS (equivalent to 4 mg of aspirin), which was instilled six-times a week. Cumulative recurrence rates of polyps compared with controls were 6.9 versus 51.3% at year 1, 44.9 versus 84.8% at 3 years and 65 versus 93.5% at 6 years. Topical LAS worked for all nasal polyp patients, and no significant differences could be elicited between aspirin-sensitive and aspirin-tolerant patients, within the group or compared with age-matched, nonrandomized controls.

The second was a 3-year follow-up study on 49 polyp patients who underwent a medical polypectomy and were subsequently started on intranasal LAS as described above. Cumulative percentages of patients requiring surgical intervention were 3.8% at 6 months, 13.1% at 1 year and 32% after 3 years. Figures for the control group were 51.3 and 85% at year 1 and 3, respectively. Once again, no differences could be shown between aspirin-sensitive and aspirin-tolerant patients.

These studies have been criticized for their lack of rigor, being unblinded and without proper randomized controls.

To examine this more rigorously a small, prospective, randomized, double-blind, placebo controlled, crossover trial was undertaken [51]. Twenty aspirin-sensitive patients confirmed by intranasal challenge were randomized to receive topical lysine aspirin (equivalent to 16 mg of aspirin) every 48 h or placebo for 6 months before crossover, with a month's washout period on betamethasone nose drops between the two phases. Polyp growth was monitored in the clinic using acoustic rhinometry, and nasal inspiratory peak flow was also recorded daily, by the patients. After withdrawals and dropouts, data on 11 patients were analyzed. This did not reveal any significant clinical benefit to patients receiving topical lysine aspirin compared with placebo. Patients showed a steady deterioration in their clinical condition, which was similar on both real and placebo therapy. Despite the failure to demonstrate clinical benefit, tissue studies showed a significant improvement at a microscopic level. Cysteinyl LT1 (CysLT1) receptors were upregulated in nasal biopsies of AERD patients, and the percentages of mucosal CD45+ leukocytes expressing CysLT1 receptors were significantly ($p < 0.0001$) elevated in aspirin-sensitive but not in aspirin-tolerant patients [53]. After using LAS intranasally, there was a reduction in CysLT1 receptors after 2 weeks, maintained

Table 4. Nasal lysine aspirin in aspirin-tolerant nasal polyposis.

Study (year)	Type of trial	Dose (aspirin equivalent mg)	Regimen	Controls (n)	Period of study (months)	Outcome measures	Results	Ref.
Patriaca <i>et al.</i> (1991)	Prospective, with controls	2	Once/week	15 (61)	24	Relapse of polyps	Relapse rate significantly less	[49]
Scadding <i>et al.</i> (1995)	Prospective, self-control (opposite nostril acted as control)	2	Once/week	20 (20)	15	Symptom score Acoustic rhinometry Rigid nasendoscopy	Less polyp tissue on LAS side	[54]
Nucera <i>et al.</i> (2000)	Prospective, with controls	4	six-times/week	62 (61)	72	Recurrence of nasal polyps	Relapse rate significantly less	[50]
Parikh A and Scadding GK, submitted	Prospective, randomized, double-blind, placebo controlled, parallel groups	16	Once/week	20 (20)	3–33	AcR Nasendoscopy Smell test (UPSIT) NIPF PEFR QOL	No difference between the groups on all counts apart from QOL, which scored worse in the LAS group	[Pers. COMM.]

AcR: Acoustic rhinometry; NIPF: Nasal inspiratory peak flow (l/min); PEFR: Peak expiratory flow rate (litres/min); QOL: Quality of life; UPSIT: University of Pennsylvania Smell Identification test.

at 6 months, compared with saline placebo. It was concluded that further work with a different dose and regimen was needed to explore any possibility for clinical improvement.

Subsequently, an open, n = 1 study has shown clinical effectiveness of LAS [52]. Polyp patients on standard therapy, but poorly controlled nasal and chest symptoms were recruited and challenged with nasal lysine aspirin. If positive, then they were given daily intranasal lysine aspirin with the dose increased in a stepwise manner until they were taking topical LAS equivalent to 37.8 mg aspirin per day. Significant improvement was shown in nasal airflow, nasal nitric oxide levels and reduction in polyp size after 3 months of therapy, compared with their performance in the 3 months prior to its use, when all other medication was identical. Peak expiratory flow rate, a measure of lower airways function, did not decrease, demonstrating the safety of this dose with respect to asthma.

Most recently, an audit of 121 aspirin-sensitive nasal polyp patients, 105 of whom were treated with intranasal lysine aspirin in gradually increasing doses following positive lysine aspirin challenge, has provided further evidence of effectiveness [HOWE *ET AL*, IN PRESS]. The final doses ranged from 7 to 250 mg aspirin equivalent, but most took 75 mg aspirin equivalent daily. Treatment was associated with subjective symptomatic improvement or stabilization in 60 of 78 patients at 3 months and 19 of 27 at 12 months, giving a number needed to treat of less than 5.5.

Nasal inspiratory peak flow, olfaction, exhaled and nasal nitric oxide levels were significantly improved ($p < 0.05$ for all). Patients with positive skin prick tests and those with later

onset (>40 years) AERD improved more than nonatopics and those with early onset AERD.

Asthma outcomes over 1 year were assessed by questionnaire in 22 patients on lysine aspirin and in 20 who were positive on challenge but who either refused treatment or took it only briefly (less than or equal to 3 months). There was a significant decrease in emergency visits ($p = 0.0182$), hospitalization ($p = 0.0074$) and oral steroid use ($p = 0.004$) in those on nasal lysine aspirin for a year.

Gastrointestinal side effects occurred in 3.8% lower than those reported for oral aspirin therapy.

Use of aspirin in aspirin-tolerant patients (TABLE 4) [49,50,54]

The initial study on the use of topical LAS in aspirin-sensitive nasal polyp patients, also explored its role in aspirin-tolerant patients with nasal polyps [49]. Fifteen aspirin-tolerant nasal polyp patients receiving topical LAS were compared with a control group of 61 aspirin-tolerant nasal polyp patients who did not receive any topical treatment. Both groups were followed for 24 months with 3 monthly examinations and measurements. There was no polyp recurrence in the aspirin-tolerant group receiving topical LAS compared with 67% of the aspirin-tolerant controls. None of patients had any side effects nor did their asthma deteriorate.

Soon thereafter work was published suggesting similar benefits of using topical LAS in aspirin-tolerant patients with nasal polyps [54]. The dose of LAS tried was equivalent to 2 mg of aspirin once a week unilaterally and the other side of the nose used as a comparator. Polyp recurrence was delayed in all

18 patients, with 8 patients remaining symptom free after 15 months. However, spill over between the two nostrils was a possible confounding factor.

The results of two long-term studies that included aspirin-tolerant nasal polyp patients have already been discussed above [50]. As shown by the figures above, topical LAS also seemed to benefit this group of patients in open studies.

Since these initial works, there was a paucity of research on the subject of topical LAS in aspirin-tolerant nasal polyposis until recently when a prospective, randomized, double-blind placebo-controlled parallel group trial was undertaken [PARIKH A & SCADDING GK, SUBMITTED]. Aspirin tolerance was confirmed on negative intranasal lysine aspirin challenge. Study parameters included rigid nasendoscopy, nasal inspiratory peak flow rate, acoustic rhinometry, visual analog scale, sense of smell, peak flow rate and quality of life.

Forty aspirin-tolerant patients were randomized into two groups receiving either topical nasal LAS equivalent to 16 mg of aspirin once a week or placebo. Five patients did not complete the trial, with four lost to follow-up and one in the placebo group noticing deterioration in asthma. Statistical analysis for the remaining patients (16: LAS group; 19: placebo group) showed a gradual deterioration in their nasal state over time. We conclude that in patients with aspirin-tolerant nasal polyps, intranasal lysine aspirin at this dose once a week in addition to intranasal corticosteroids is not effective in reducing polyp growth. The effect of a higher dose has not been studied.

Expert commentary

Many patients with nasal polyps and asthma are unaware whether they are liable to a severe, life-threatening reaction if they take aspirin or other COX-1 inhibitors. In the UK, primary care practitioners usually warn all asthma subjects to avoid aspirin – while playing safe, this means that the therapeutic actions of this very cheap drug aspirin for analgesia and anti-inflammation, or for long-term protection versus cardiovascular disease and many tumors cannot be utilized by many who are aspirin tolerant. It would be sensible to use a relatively quick and safe method to detect aspirin sensitivity: a blood test would be ideal, but unfortunately none is yet sufficiently accurate. The lysine aspirin nasal challenge is the next best option, being relatively quick and safe, providing that patients are carefully chosen while retaining good sensitivity and specificity. At present, lysine aspirin is not obtainable in the UK or USA, but is purchasable over the counter in France and Spain and can be imported for use on a named patient basis.

AERD is a chronic inflammatory disorder of the respiratory tract in which despite avoidance of aspirin and NSAIDs, mucosal inflammation of the upper and lower respiratory tracts persists and progresses in the majority of patients, despite use of guideline-directed treatment [55]. There is little doubt that regular oral aspirin can alter disease progression, but the dose needed is usually 300 mg or more and side effects, particularly gastrointestinal ones, are common, with occasional severe bleeding. Oral desensitization is also a difficult and dangerous

procedure, requiring hospital admission for days, intravenous lines and rescue therapy.

Topical nasal lysine aspirin has been shown to alter cysteinyl leukotriene receptors, in a disease where leukotrienes are important mediators, in a double-blind, placebo-controlled trial [53]. Nasal lysine aspirin also improved clinical outcomes in less rigorous studies. Although formal evidence is still weak, a larger controlled therapeutic trial is needed, together with further investigation of the underlying pathophysiological changes since the mechanism of action of LAS used in this way is uncertain, and it is unlikely that patients taking 75 mg nasally are fully systemically desensitized, though they are tolerating a dose of aspirin that is optimal for cardiovascular protection [56]. In this respect, LAS is likely to be superior to the NSAID Ketorolac (the only topical form available in the USA), which is detrimental to the cardiovascular system; and to oral desensitization, where the higher doses used [57] are not cardioprotective. Aspirin itself is an anti-inflammatory and this may be relevant; however, topical aspirin was not effective in a double-blind study in aspirin-tolerant polyps (although earlier uncontrolled studies did suggest benefit), which makes this simple explanation unlikely. Lysine itself has activity against herpes simplex which may be implicated in AERD pathogenesis [58].

Five-year view

The significant morbidity and mortality of AERD are becoming appreciated: it is a leading cause of severe chronic upper airways disease. Better therapies are needed, thus clinical trials of expensive molecules such as anti-IgE and anti-IL5 have been and are being undertaken by pharmaceutical companies. While it is likely that these will show efficacy, their cost and complexity means that unavailability for the majority of sufferers is likely on the grounds of cost per quality of life unit.

Nasal lysine aspirin therapy shows promise, being probably effective, safe and likely to confer benefits outside the respiratory tract, such as a reduction in cardiovascular events [59] and several cancers [60] – with the 75 mg dose now used, since this swallowed from the back of the nose. It is also very cheap. Funding a proper large-scale double-blind, placebo-controlled trial would make sense, especially as concomitant investigation using nasal scrapings and/or biopsies that might improve our imperfect understanding of this fascinating disease. The observation that nasal lysine aspirin improved control of concomitant asthma requires confirmation in a prospective study, but would allow improved asthma care in a difficult group of patients without adding to their steroid load.

Further work on lysine aspirin deserves proper funding so that its place in guidelines can be established.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Failure to control eosinophilic inflammation in the upper respiratory tract.
- Causes significant symptoms and reduction in quality of life, work/school ability in sufferers.
- and leads to costly repeated surgical interventions, or to repeated use of oral corticosteroids with their detrimental side effects.
- Lysine aspirin presents a possible therapeutic option in aspirin-sensitive subjects with nasal polyposis and asthma.
- But needs further investigation in proper double-blind, placebo-controlled studies.

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