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Aspirin desensitisation therapy for aspirin-intolerant chronic rhinosinusitis (Protocol)

Vaidyanathan S, McKean S, Lipworth BJ

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[Intervention Protocol]

Aspirin desensitisation therapy for aspirin-intolerant chronic rhinosinusitis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of oral, inhaled or intranasal aspirin desensitisation, as monotherapy or as adjunctive therapy, in adult patients with aspirin intolerant chronic rhinosinusitis, with or without concomitant asthma. We will evaluate subjective and objective parameters of nasal and lower airway function, quality of life and adverse event profiles.

BACKGROUND

Chronic rhinosinusitis is a common respiratory disorder involving inflammation of the lining of the nose and paranasal sinuses. It is characterised by nasal obstruction, rhinorrhoea (anterior or posterior nasal discharge), facial discomfort and often a reduction in the sense of smell, which last for more than 12 weeks (Fokkens 2007; Scadding 2008). There are limited data on the prevalence of chronic rhinosinusitis in the general population, but estimates vary between 2% and 16% in Europe and the United States (Bachert 2009; Fokkens 2007). In the 2003 US National Health Survey, nearly 30 million CRS sufferers were identified (Wallace 2008). The annual treatment costs of chronic rhinosinusitis are estimated to be in the billions and this is likely to underestimate indirect costs from reduced work performance, sickness absenteeism and lost days from work (Ray 1999; Fokkens 2007). Patients with chronic rhinosinusitis have been shown to report significantly lower quality of life scores than those patients with congestive heart failure, angina, chronic obstructive pulmonary disease or chronic back pain (Gliklich 1995).

Of note, 5% to 8% of patients with chronic rhinosinusitis and nasal polyps will be intolerant to aspirin (acetylsalicylic acid) and non-steroidal anti-inflammatory drugs (NSAIDs) and almost invariably have associated asthma. This triumvirate of disorders is often referred to as the 'aspirin triad' or 'Samter's triad' (Samter 1968). It is known by several acronyms and names such as aspirin-induced/intolerant asthma (AIA), aspirin-induced/intolerant rhinosinusitis (AIR), aspirin sensitive asthma (ASA), aspirin hypersensitivity and aspirin exacerbated respiratory disease (AERD). Hereon, we shall use the term aspirin-induced/intolerant rhinosinusitis (AIR).

Description of the condition

Prevalence and epidemiology

A meta-analysis showed that the prevalence of aspirin sensitivity in the general population may be as high as 22% if oral aspirin challenge tests are used as the diagnostic yardstick instead of patient history (Jenkins 2004). Moreover, there is almost a 100% cross-sensitivity to common over-the-counter NSAIDs (Jenkins 2004; Melillo 2001). Aspirin sensitivity affects about 10% of adults with chronic asthma and in patients with aspirin sensitivity, 36% to 96% have nasal polyposis as evidenced by endoscopic or radiographic changes (Fokkens 2007).

Aetiopathogenesis

The pathogenetic mechanism of AIR and asthma is complex and is not fully understood. Common hypotheses include an imbalance in the arachidonic acid pathway causing an overproduction in leukotrienes in genetically predisposed phenotypes (Jenneck

2007). It is postulated that the inhibition of the COX1 enzyme by aspirin (or related substances) leads to subsequent inflammatory cell activation, and the release of both lipid and non-lipid mediators (Stevenson 2006). A significantly lower generation of PGE2 and COX2 expression in the nasal and sinus mucosa has been reported (Kowalski 2000; Picado 1999). This could contribute to the development of the severe eosinophilic inflammation characteristic of AIR patients.

Clinical presentation and diagnosis

AIR usually presents in the third and fourth decades and is more common in females and in non-atopic individuals (Scadding 2008). It may present initially as non-specific rhinorrhoea and nasal congestion and progresses over the next decade or so to aspirin sensitivity, asthma and nasal polyposis (Szczeklik 2000). The intolerance/sensitivity can manifest in a varied fashion and can occur as any combination of symptoms, ranging from a subtle worsening of rhinorrhoea, hyposmia, post-nasal discharge, congestion, cough and bronchospasm to, in rare cases, respiratory arrest and shock. The manifestation within an individual, however, is usually consistent, with most reactions occurring within 20 to 120 minutes of ingestion of aspirin or a NSAID (Scadding 2008). The two most frequent clinical presentations of aspirin hypersensitivity are aspirin-induced bronchial asthma/rhinosinusitis and aspirin-induced urticaria/angioedema. They occur only rarely in combination (Jenneck 2007).

Typically, the presence of aspirin intolerance makes the upper and lower airways disease severe, persistent and treatment resistant (Fokkens 2007). Patients with AIR have a higher frequency of hospitalisations and emergency department visits than tolerant patients (Berges-Gimeno 2002). Their illness is recalcitrant to medical and surgical treatment and they are often either steroid dependant or unresponsive (Scadding 2008). In a pan-European survey of AIR, inhaled corticosteroids or oral corticosteroids were used by 80% of afflicted patients with a mean daily dose of 8 mg of oral prednisolone (Szczeklik 2000). Endoscopic sinus surgery outcomes are also less successful in AIR patients compared with aspirin tolerant patients, with more frequent and earlier relapses (Gosepath 1999).

The diagnosis of aspirin sensitivity relies upon either a clear history of two or more aspirin/NSAID induced reactions and/or on aspirin challenge, which can be oral, inhaled or intranasal (Scadding 2008). Establishing a diagnosis of aspirin intolerance is important. It provides the patient with a host of common drugs that must be avoided, diagnoses a particularly severe and recalcitrant form of disease phenotype and allows a choice of specific therapy such as leukotriene modifiers or aspirin desensitisation (Fokkens 2007). Unfortunately, *in vitro* tests lack sufficient sensitivity and specificity to diagnose AIR accurately (Scadding 2008). While aspirin challenge tests are recommended as the investigations of choice, there is little evidence for the existence of subclinical aspirin sensitivity (Killen 2003) and therefore they cannot be recommended

as a screening test. The use of provocation testing is primarily confined to research settings or to patients undergoing desensitisation. Due to the risk of anaphylaxis, provocation testing must be carried out by trained personnel in facilities with full resuscitation protocols (Scadding 2008).

Oral aspirin challenge with placebo control is widely used, but is time consuming (it can be three days long), and may provoke severe bronchospastic and anaphylactoid reactions. Moreover, a negative oral challenge cannot by itself rule out AIR. Indeed the possibility of false-negative responses increases when diagnostic provocation tests with aspirin are carried out in asthmatics being treated with corticosteroids or during symptom-free intervals (Melillo 2001). However, when endpoints such as a 20% reduction in forced expiratory volume in 1 second (FEV1), or characteristic extrathoracic symptoms (such as severe rhinorrhoea and nasal congestion), are used oral aspirin challenges have a sensitivity of 89% and specificity of 93% (Nizankowska-Mogilnicka 2007).

Inhalation or nasal challenge with lysine aspirin (L-ASA) is becoming the preferred method. L-ASA is more soluble than aspirin (40% versus 0.3%), is non-irritant, and is well tolerated when inhaled (Melillo 2001). Nasal challenge with L-ASA is equally sensitive and specific (95.7% and 86.7%, respectively), but a negative test does not preclude aspirin sensitivity (Nizankowska 2000). Its negative predictive value is as low as 78.6% and an oral challenge is recommended after a negative nasal test (Nizankowska 2000). Lastly, irrespective of challenge results, aspirin sensitivity should always be suspected in patients with severe nasal polyposis, especially those with recurrent polyps and steroid dependent refractory asthma (Scadding 2008).

Description of the intervention

Treatment options

Prevention

Patients should be warned to avoid all drugs with COX-1 inhibitor activity. Although selective COX-2 inhibitors and paracetamol appear to be safe, the first dose should preferably be administered in hospital under monitoring (Scadding 2008). The role of avoiding preservatives, additives and high salicylate foods is controversial, with some benefit reported in open studies (Scadding 2008).

Leukotriene pathway modification

There is evidence that leukotriene modifiers like montelukast ameliorate nasal symptoms, decrease nasal response to an aspirin challenge and reduce the need for corticosteroids (Lee 2004; Micheletto 2004; Tohda 2002). In an uncontrolled prospective study of 678 patients with AIR, leukotriene modifiers alone or in combination blocked lower respiratory tract reactions rather than

upper respiratory symptoms during aspirin challenge in some patients. There was no change in the overall rate of positive challenge results (White 2005). Leukotriene modifiers are only partially effective and patients often experience breakthrough nasal and bronchospastic symptoms despite treatment (Volkman 2002).

Aspirin desensitisation

Aspirin desensitisation is an important therapeutic option for patients who have inadequately controlled AIR and/or asthma despite treatment with topical corticosteroids and leukotriene-modifying drugs. Aspirin desensitisation reduces the reactions to aspirin by repeated and increasing exposure to prudent daily doses until all reactions cease. Just like provocation testing, desensitisation can be performed via the oral, endonasal or inhalational routes.

Aspirin desensitisation has been described as a treatment modality since 1922 (Widal 1987). In 1977, Bianco et al tried the bronchial provocation test with L-ASA in asthmatic patients intolerant to aspirin, and observed the existence of a refractory period post-challenge (Bianco 1977). At the end of the trial (within 20 days), all patients tolerated 500 mg of aspirin by mouth. Several author groups have since reported successful desensitisation with good clinical efficacy, a low risk-profile and high cost-effectiveness (Gollapudi 2004). There is some evidence that desensitisation may be more effective for rhinosinusitis symptoms than for lower airway symptoms, but overall patient hospitalisations and emergency department visits are reduced (Morwood 2005).

A typical oral regime will consist of gradually increasing doses of oral aspirin, and desensitisation takes a few days to achieve. Different authors have recommended various regimes and dosages ranging from 100 mg to 1300 mg of oral aspirin so as to maintain a reduction of polyp size, improvement in olfaction and need for revision surgery, and improvement in lower airway outcomes (Lee 2007; Kowalski 1986; Rozsasi 2008; Stevenson 1996). The European Network of Aspirin-Induced Asthma (AIANE) have described these procedures used to obtain desensitisation as 'adaptive deactivation' to distinguish them from the desensitisation obtained by specific immunotherapy in allergic asthma (Melillo 2001). 'Rush deactivation' is obtained in two days by administering L-ASA until induction of tolerance. 'Individual dose titration' is a combination of inhalation and oral administration of aspirin, and complete tolerance (which means that a single dose of 500 mg of aspirin is safely tolerated) is generally induced in 12 days. Endonasal desensitisation has also been successfully carried out using the topical application of L-ASA for the specific treatment of AIR (Nucera 2000; Patriarca 1991). One author group have reported a lack of efficacy with a regimen of 16 mg of topical L-ASA or placebo instilled intranasally every 48 hours for six months (Parikh 2005). However, the same group reported improvements in polyp scores, peak nasal inspiratory flow rates and nasal nitric oxide levels using an endonasal regimen of 30 mg/ml L-ASA to each side in a dose ramp from 2 mg/day, increased every two or three days up to a maximum of 54 mg/day (Ogata 2007).

Endonasal desensitisation may be sensitive to local factors such as nasal polyp size, mucociliary clearance, or to the concentration or regime of L-ASA.

Initial desensitisation by any route must be followed by maintenance dosing, as this deactivated state is only sustained for two to five days after cessation of aspirin. After this, one can ingest aspirin or NSAIDs on an indefinite basis by taking a maintenance dose of aspirin without any serious adverse effects in many cases (Szczeklik 2003). With appropriate monitoring equipment and adequately trained personnel, this can be done as an outpatient regimen (Macy 2007). It is important to note that if doses of aspirin are missed for any reason for more than 48 hours, then a repeat graded desensitisation will need to be done, or else severe reactions may be provoked. Inpatient desensitisation has been recommended for patients with the following risk factors: beta-blocker use, recent myocardial infarction, severe asthma, history of severe or life threatening aspirin or NSAID reaction, or any medical condition or drug treatment regimen that would make the management of severe asthma or anaphylactoid reaction difficult (Macy 2007). Pre-treatment with a cysteinyl leukotriene modifier such as montelukast, zileuton (or both) significantly reduces the incidence and severity of any aspirin-induced bronchospastic reactions (White 2005).

With oral and inhaled desensitisation, there is a small but pertinent risk of anaphylactoid and bronchospastic reactions. Full cardiopulmonary resuscitation equipment must be available in the centre conducting desensitisation, and the patient must be under the supervision of a practitioner with advanced life-support training for two to three hours. The risks of desensitisation also include cutaneous reactions and gastrointestinal symptoms (dyspepsia, gastritis or haemorrhage). These are observed in about 20% of patients treated with aspirin (Fokkens 2007; Morwood 2005). There should be a protocol for dealing with aspirin-induced reactions; for example, ocular reactions which can be treated with topical antihistamines, gastrointestinal symptoms with proton pump inhibitors or H2 blockers, urticaria/angioedema with adrenaline and steroids, and bronchospasm with inhaled beta agonists etc. (Stevenson 2006). Oral aspirin desensitisation followed by maintenance daily dosing may cause significant side effects, including gastrointestinal bleeding at high doses. There is some evidence to suggest that oral doses as low as 100 mg daily may be effective for maintenance therapy and this could potentially circumvent some of the adverse effects associated with currently recommended doses of 300 mg (Gosepath 1999).

How the intervention might work

While the pathophysiologic mechanisms of desensitisation remain obscure, a decrease in the number of nasal inflammatory cells expressing the Cyst-LT1 receptor remains one of the possibilities (Szczeklik 2006). Peripheral blood monocytes from desensitised patients synthesise less thromboxane B2, a major product of COX-

1 and -2 (Szczeklik 2003). Another possibility is that aspirin desensitisation interferes with Cyst-LT1 receptors or intracellular signalling mechanisms in such a way that although leukotrienes are available, they cannot induce an effector event (Szczeklik 2003). The precise mechanisms of adaptive deactivation and oral desensitisation with aspirin are still unknown. However, refractoriness to a bronchospasm inducing stimulus is a phenomenon which is unique in secondary types of asthma, e.g. exercise-induced asthma. Similarly, AIR patients also exhibit a refractory period after aspirin challenge (Picado 2002). During this time further doses do not lead to a deterioration of their condition.

Why it is important to do this review

Most of the evidence for desensitisation is anecdotal and uncontrolled, with varied regimens, routes of administration (oral, endonasal) and dosages. It is important to evaluate the efficacy and safety of aspirin desensitisation in patients with the aspirin triad, as treatment options for this severely afflicted group are minimal. Clinical benefits reported in long-term uncontrolled studies include reduction in nasal obstruction, decreased polyp size, improvement in the sense of smell, decreased incidence of respiratory and sinus infections, reduced need for nasal corticosteroids, and a reduction in 'rescue' systemic steroids and sinus and polyp surgery episodes (Rozsasi 2008; Stevenson 1996). In particular, patients with therapy-resistant rhinosinusitis and recurrent nasal polyps (Jenneck 2007), and those on long-term systemic steroids might benefit from desensitisation. Additional benefits in the form of cross-tolerance to other NSAIDs may also develop as a result of treatment (Simon 2004). Benefits of desensitisation might therefore also be apparent in patients with concomitant illnesses, such as coronary artery disease or those requiring NSAIDs for bone and joint conditions. There were no systematic reviews on aspirin desensitisation in the literature at the time of writing this protocol.

OBJECTIVES

To assess the effectiveness of oral, inhaled or intranasal aspirin desensitisation, as monotherapy or as adjunctive therapy, in adult patients with aspirin intolerant chronic rhinosinusitis, with or without concomitant asthma. We will evaluate subjective and objective parameters of nasal and lower airway function, quality of life and adverse event profiles.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials.

Types of participants

We will include adult participants over 16 with a clinical diagnosis of chronic rhinosinusitis, with or without nasal polyposis, according to the EPOS 2007 guidelines (Fokkens 2007) and aspirin intolerance diagnosed by history and/or a positive nasal/bronchial/oral aspirin challenge (as defined by trialists), with or without asthma. We will not include studies specifically looking at intolerance to and desensitisation with NSAIDs alone.

Types of interventions

Any oral/inhaled/endonasal aspirin desensitisation, any dosages, regimens or frequency.

- Aspirin desensitisation versus no intervention.
- Aspirin desensitisation versus placebo.
- Aspirin desensitisation plus any other topical or systemic therapies for chronic rhinosinusitis currently in clinical use versus placebo.
- Aspirin desensitisation versus other topical or systemic therapies for chronic rhinosinusitis currently in clinical use.

Types of outcome measures

Primary outcomes

1. Validated nasal symptom scores. If standard nasal symptom scores with the same metric are used then pooling will be considered appropriate. These data will be treated as continuous. If different instruments are used, then a composite nasal symptom score will be derived as a percentage of the maximum symptom score possible and treatment groups compared. However, data will be interpreted cautiously in this scenario (Puhan 2006).

2. Severe or fatal adverse reactions necessitating withdrawal from study or cessation of treatment. These will include any bleeding events requiring transfusions or surgery, any gastrointestinal haemorrhage, severe bronchospasm requiring oral or intravenous steroids, anaphylaxis requiring epinephrine, angioedema, hospitalisation for outpatient treatment etc.

Secondary outcomes

1. Number of sinus infections.
2. Number of rescue courses of oral corticosteroids.
3. Number of courses of antibiotics.
4. Number of episodes of sinus surgery or polypectomy.
5. Reduction in medication dosage.
6. Validated quality of life questionnaire scores. If standardised tools such as SNOT-20, SNOT-22, RSOM-31 or RQLQ are

used, then pooling will be considered for the same instrument. The data will be treated as continuous. If different instruments are used, then a composite quality of life score will be derived as a percentage of the maximum possible score and treatment groups compared.

7. Change in nasoendoscopic polyp scores.
8. Change in olfaction.
9. Change in paranasal sinus CT scores.
10. Change in objective measures of upper airway patency including peak nasal inspiratory flow rate, nasal volume estimated by acoustic rhinometry, nasal airway resistance by rhinomanometry.
11. Change in nasal nitric oxide.
12. Change in tissue or systemic eosinophilia, eosinophilic cytokines like IL-5, eotaxin, ECP.
13. Change in lower airway symptoms, spirometry, tidal nitric oxide and quality of life scores. Symptom scores and quality of life scores for asthma will be dealt with in a similar fashion to the upper airway.

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear; and we will arrange translations of papers where necessary.

Electronic searches

We will search the following bibliographic databases:

- the Cochrane Ear, Nose and Throat Disorders Group Trials Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue);
- PubMed;
- EMBASE;
- CINAHL;
- AMED;
- ISI Web of Science;
- BIOSIS Previews;
- CAB Abstracts;
- LILACS;
- KoreaMed;
- IndMed;
- PakMediNet;
- China National Knowledge Infrastructure;
- mRCT (the metaRegister of Controlled Trials);
- Google.

Subject strategies for databases will be modelled on the search strategy designed for CENTRAL. Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search

strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in *The Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. ([Handbook 2008](#))).

CENTRAL search strategy

#1 MeSH descriptor Rhinitis explode all trees with qualifier: DT
#2 MeSH descriptor Rhinitis explode all trees with qualifier: TH
#3 MeSH descriptor Sinusitis explode all trees with qualifier: TH
#4 MeSH descriptor Sinusitis explode all trees with qualifier: DT
#5 rhinosinusitis OR nasosinusitis OR sinusitis OR rhinitis OR pansinusitis OR ethmoiditis OR ethmoiditis OR sphenoiditis
#6 MeSH descriptor Chronic Disease explode all trees
#7 MeSH descriptor Recurrence explode all trees
#8 chronic OR persis* OR recurren*
#9 (#1 OR #2 OR #3 OR #4 OR #5)
#10 (#6 OR #7 OR #8)
#11 (#9 AND #10)
#12 MeSH descriptor Aspirin explode all trees
#13 Aspirin OR Acetyl* OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin
#14 ASA OR AIA OR AERD
#15 (#12 OR #13 OR #14)
#16 (#11 AND #15)
#17 MeSH descriptor Desensitization, Immunologic explode all trees
#18 MeSH descriptor Respiratory Hypersensitivity explode all trees with qualifier: DT
#19 MeSH descriptor Respiratory Hypersensitivity explode all trees with qualifier: TH
#20 (sensitiv* OR desensitiz* OR desensitis* OR hypersensit*)
#21 (#17 OR #18 OR #19 OR #20)
#22 (#16 AND #21)

Searching other resources

We will scan reference lists of identified publications for additional trials and contact authors if necessary. PubMed, TRIPdatabase, NLH ENT & Audiology Specialist Library and Google will be searched to retrieve existing systematic reviews possibly relevant to this systematic review, so that we can scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

SV and SM will assess the studies to be included independently to identify studies which meet the criteria outlined above. If there is disagreement we will resolve this by discussion and in the final instance by arbitration by BL.

Data extraction and management

We will extract data onto standardised, pre-piloted forms. Where data are missing or unclear, we will attempt to contact the trial author(s). Data will be extracted so as to allow an intention-to-treat analysis.

Assessment of risk of bias in included studies

We will evaluate the quality of studies using a 'Risk of bias' table for each study. This allows an assessment of each study under six domains: sequence generation, blinding, incomplete outcome data, allocation concealment, selective outcome reporting and 'other issues'. The first part of the tool is a descriptive entry which summarises each included study and from which judgements of bias can be made. The second part involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of 'yes' indicates low risk of bias, 'no' indicates high risk of bias, and 'unclear' indicates unclear or unknown risk of bias. The results of this bias assessment will be displayed as a 'Risk of bias' summary figure generated by RevMan 5.0 software ([Handbook 2008](#); [RevMan 2008](#)).

Data synthesis

Data will be analysed by the intention-to-treat principle. If data are comparable and of sufficient quality we will combine to give a summary measure of effect, otherwise data will be treated as mentioned above or not be combined. We will perform statistical analysis using Review Manager 5.0 ([RevMan 2008](#)). For dichotomous outcomes we will calculate a relative risk (RR). We will use a weighted mean difference (WMD) or standardised mean difference (SMD) for continuous outcomes as appropriate. We will assess heterogeneity using the Chi² test and I² statistic available in RevMan 5. We will use a fixed-effect model where non-significant heterogeneity is found between studies. If great heterogeneity in studies is found then we will use a random-effects model.

If data permit we will conduct the following subgroup analyses:

- CRS without asthma;
- CRS with asthma;
- Previous endoscopic sinus surgery.

We will use study quality in sensitivity analyses.

REFERENCES

Additional references

Bachert 2009

Bachert C, Van Bruaene N, Toskala E, Zhang N, Olze H, Scadding G. Important research questions in allergy and related diseases: 3-chronic rhinosinusitis and nasal polyposis - a GA2LEN study. *Allergy* 2009;**64**(4):520–33.

Berges-Gimeno 2002

Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma, and Immunology*. 2002/11/28 2002; Vol. 89, issue 5: 474–8. [1081–1206: (Print)]

Bianco 1977

Bianco S, Robuschi M, Petrini G. Aspirin-induced tolerance in a patient with aspirin induced asthma. *IRCS Journal of Medical Science* 1977; Vol. 5:129–36.

Fokkens 2007

Fokkens W, Lund V, Mullol J, European Position Paper on Rhinosinusitis and Nasal Polyps group. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology Supplement* 2007, issue 20:1–136. [1013–0047: (Print)]

Gliklich 1995

Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngology - Head and Neck Surgery* 1995; Vol. 113, issue 1:104–9. [0194–5998: (Print)]

Gollapudi 2004

Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004; Vol. 292, issue 24:3017–23. [1538–3598: (Electronic)]

Gosepath 1999

Gosepath J, Hoffmann F, Schafer D, Amedee RG, Mann WJ. Aspirin intolerance in patients with chronic sinusitis. *ORL; Journal of Oto-Rhino-Laryngology and its Related Specialties*. 1999/05/15 1999; Vol. 61, issue 3:146–50. [0301–1569: (Print)]

Handbook 2008

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Jenkins 2004

Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; Vol. 328, issue 7437:434. [1468–5833: (Electronic)]

Jenneck 2007

Jenneck C, Juergens U, Buecheler M, Novak N. Pathogenesis, diagnosis, and treatment of aspirin intolerance. *Annals of Allergy, Asthma, and Immunology*. 2007/07/27 2007; Vol. 99, issue 1:13–21. [1081–1206: (Print)]

Killen 2003

Killen JW, Wilson JA, Gibson GJ. Subclinical aspirin sensitivity in subjects with nasal polyposis. *Clinical Otolaryngology and Allied Sciences*. 2003/11/18 2003; Vol. 28, issue 6:539–44. [0307–7772: (Print)]

Kowalski 1986

Kowalski ML, Grzelewska-Rzymowska I, Szmidt M, Rozniecki J. Clinical efficacy of aspirin in “desensitised” aspirin-sensitive asthmatics. *European Journal of Respiratory Diseases*. 1986/10/01 1986; Vol. 69, issue 4: 219–25. [0106–4339: (Print)]

Kowalski 2000

Kowalski ML. Rhinosinusitis and nasal polyposis in aspirin sensitive and aspirin tolerant patients: are they different? *Thorax*. 2000/09/19 2000; Vol. 55 Suppl 2:S84–6. [0040–6376: (Print)]

Lee 2004

Lee DK, Haggart K, Robb FM, Lipworth BJ. Montelukast protects against nasal lysine-aspirin challenge in patients with aspirin-induced asthma. *European Respiratory Journal* 2004; Vol. 24, issue 2:226–30. [0903–1936: (Print)]

Lee 2007

Lee JY, Simon RA, Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology*. 2007/01/09 2007; Vol. 119, issue 1:157–64. [0091–6749: (Print)]

Macy 2007

Macy E, Bernstein JA, Castells MC, Gawchik SM, Lee TH, Settipane RA, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. *Annals of Allergy, Asthma, and Immunology* 2007; Vol. 98, issue 2:172–4. [1081–1206: (Print)]

Melillo 2001

Melillo G, Balzano G, Bianco S, Dahlen B, Godard P, Kowalsky ML, et al. Report of the INTERASMA Working Group on Standardization of Inhalation Provocation Tests in Aspirin-induced Asthma. Oral and inhalation provocation tests for the diagnosis of aspirin-induced asthma. *Allergy*. 2001/09/12 2001; Vol. 56, issue 9:899–911. [0105–4538: (Print)]

Micheletto 2004

Micheletto C, Tognella S, Visconti M, Pomari C, Trevisan F, Dal Negro RW. Montelukast 10 mg improves nasal function and nasal response to aspirin in ASA-sensitive asthmatics: a controlled study vs placebo. *Allergy* 2004; Vol. 59, issue 3: 289–94. [0105–4538: (Print)]

Morwood 2005

Morwood K, Gillis D, Smith W, Kette F. Aspirin-sensitive asthma. *Internal Medicine Journal* 2005; Vol. 35, issue 4: 240–6. [1444–0903: (Print)]

Nizankowska 2000

Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for

- diagnosis of aspirin-induced asthma. *European Respiratory Journal* 2000; Vol. 15, issue 5:863–9. [0903–1936: (Print)]
- Nizankowska-Mogilnicka 2007**
Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007; Vol. 62, issue 10: 1111–8. [0105–4538: (Print)]
- Nucera 2000**
Nucera E, Schiavino D, Milani A, Del Ninno M, Misuraca C, Buonomo A, et al. Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax*. 2000/09/19 2000; Vol. 55 Suppl 2:S75–8. [0040–6376: (Print)]
- Ogata 2007**
Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. *Journal of Laryngology and Otology*. 2007/08/19 2007; Vol. 121, issue 12:1156–60. [1748–5460: (Electronic)]
- Parikh 2005**
Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. *Laryngoscope*. 2005/08/12 2005; Vol. 115, issue 8: 1385–90. [0023–852X: (Print)]
- Patriarca 1991**
Patriarca G, Schiavino D, Nucera E, Papa G, Schinco G, Fais G. Prevention of relapse in nasal polyposis. *Lancet*. 1991/06/15 1991; Vol. 337, issue 8755:1488. [0140–6736: (Print)]
- Picado 1999**
Picado C, Fernandez-Morata JC, Juan M, Roca-Ferrer J, Fuentes M, Xaubet A, et al. Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. *American Journal of Respiratory and Critical Care Medicine*. 1999/07/03 1999; Vol. 160, issue 1:291–6. [1073–449X: (Print)]
- Picado 2002**
Picado C. Aspirin intolerance and nasal polyposis. *Current Allergy and Asthma Reports*. 2002/11/14 2002; Vol. 2, issue 6:488–93. [1529–7322: (Print)]
- Puhan 2006**
Puhan MA, Soesilo I, Guyatt GH, Schunemann HJ. Combining scores from different patient reported outcome measures in meta-analyses: when is it justified?. *Health and Quality of Life Outcomes*. 2006/12/13 2006; Vol. 4:94. [1477–7525: (Electronic)]
- Ray 1999**
Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *Journal of Allergy and Clinical Immunology* 1999; Vol. 103, issue 3 Pt 1:408–14. [0091–6749: (Print)]
- RevMan 2008**
The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.
- Rozsasi 2008**
Rozsasi A, Polzehl D, Deutschle T, Smith E, Wiesmiller K, Riechelmann H, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy*. 2008/08/14 2008; Vol. 63, issue 9:1228–34. [1398–9995: (Electronic)]
- Samter 1968**
Samter M, Beers RF, Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Annals of Internal Medicine* 1968; Vol. 68, issue 5:975–83. [0003–4819: (Print)]
- Scadding 2008**
Scadding GK, Durham SR, Mirakian R, Jones NS, Drake-Lee AB, Ryan D, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clinical and Experimental Allergy*. 2008/01/03 2008; Vol. 38, issue 2:260–75. [1365–2222: (Electronic)]
- Simon 2004**
Simon RA. Adverse respiratory reactions to aspirin and nonsteroidal anti-inflammatory drugs. *Current Allergy and Asthma Reports* 2004; Vol. 4, issue 1:17–24. [1529–7322: (Print)]
- Stevenson 1996**
Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *Journal of Allergy and Clinical Immunology*. 1996/10/01 1996; Vol. 98, issue 4: 751–8. [0091–6749: (Print)]
- Stevenson 2006**
Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *Journal of Allergy and Clinical Immunology*. 2006/10/13 2006; Vol. 118, issue 4:773–86; quiz 787–8. [0091–6749: (Print)]
- Szczeklik 2000**
Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *European Respiratory Journal* 2000; Vol. 16, issue 3:432–6. [0903–1936: (Print)]
- Szczeklik 2003**
Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *Journal of Allergy and Clinical Immunology* 2003; Vol. 111, issue 5:913–21; quiz 922. [0091–6749: (Print)]
- Szczeklik 2006**
Szczeklik A, Sanak M. The broken balance in aspirin hypersensitivity. *European Journal of Pharmacology*. 2006/02/07 2006; Vol. 533, issue 1–3:145–55. [0014–2999: (Print)]

Tohda 2002

Tohda Y, Fujimura M, Taniguchi H, Takagi K, Igarashi T, Yasuhara H, et al. Leukotriene receptor antagonist, montelukast, can reduce the need for inhaled steroid while maintaining the clinical stability of asthmatic patients. *Clinical and Experimental Allergy* 2002; Vol. 32, issue 8: 1180–6. [0954–7894: (Print)]

Volkman 2002

Volkman JA, Pontikes PJ. Leukotriene modifiers to prevent aspirin-provoked respiratory reactions in asthmatics. *Annals of Pharmacotherapy* 2002; Vol. 36, issue 9: 1457–61. [1060–0280: (Print)]

Wallace 2008

Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *Journal of Allergy*

and Clinical Immunology 2008; Vol. 122, issue 2 Suppl: S1–84. [1097–6825: (Electronic)]

White 2005

White AA, Stevenson DD, Simon RA. The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma, and Immunology*. 2005/11/11 2005; Vol. 95, issue 4: 330–5. [1081–1206: (Print)]

Widal 1987

Widal F, Abrami P, Lermoyez J. First complete description of the aspirin idiosyncrasy-asthma-nasal polyposis syndrome (plus urticaria) - 1922 (with a note on aspirin desensitization). *Journal of Asthma* 1987; Vol. 24, issue 5: 297–300. [0277–0903: (Print)]

* *Indicates the major publication for the study*

HISTORY

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CONTRIBUTIONS OF AUTHORS

Sriram Vaidyanathan - Generated protocol and subsequent revisions, and will jointly review studies. Data management and co-ordination of review progress. Guarantor of the integrity of the review.

Simon McKean - Critical revisions, intellectual content, and will jointly review studies. Data management and co-ordination of review progress.

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All authors will be responsible for writing the review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.