# Treatment of Aspirin Exacerbated Respiratory Disease with a Low Salicylate Diet: A Pilot Crossover Study

Doron D. Sommer, MD, FRCSC[1], Stephanie Hoffbauer[1], Michael Au, MD[2], Leigh J. Sowerby, MD, FRCSC[3], Michael K. Gupta, MD, FRCSC[1], and Smriti Nayan, MD, FRCSC[1]

## Abstract

*Objective.* Aspirin exacerbated respiratory disease (AERD) is comprised of aspirin/acetylsalicylic acid (ASA) sensitivity, bronchial asthma, and nasal polyposis. Treatment of this condition is challenging and may include topical/systemic steroids, endoscopic sinus surgery, and/or aspirin desensitization.

*Study Design.* A prospective crossover pilot study (n = 10) was conducted in which patients were randomized into either of 2 groups with 6 weeks of regular diet (R) or 6 weeks of a low salicylate diet (LS).

*Setting.* The study was conducted in a tertiary otolaryngology clinic.

*Subjects.* Patients with AERD were enrolled in the study.

*Methods.* Subjective (Sino-nasal Outcome Test-22 [SNOT-22], Nasal Sinus Symptom Scale [NSSS], and the Asthma Control Questionnaire-7 [ACQ-7]) and objective outcome instruments (Peri-Operative Sinus Evaluation [POSE] and Lund-Kennedy Endoscopic Score [LKES]) were used to evaluate patients at baseline, 6 weeks (at crossover), and 12 weeks.

*Results.* Wilcoxon rank sum tests demonstrated that patients on the low salicylate diet had improved scores compared to their regular diet when evaluated by 4 of the 5 outcome measures (SNOT-22 $p_{LS}$ = 0.0059, NSSS $p_{LS}$ = 0.0195, LKES $p_{LS}$ = 0.0039, POSE $p_{LS}$ = 0.005).

*Conclusion.* Results of the pilot study indicate that implementation of a low salicylate diet improves the nasal symptoms and nasal endoscopy findings of individuals with AERD. Further research is required to support these findings.

## Keywords

nasal polyps, sinusitis, asthma, salicylates, aspirin exacerbated respiratory disease, low salicylate diet

## Introduction

Samter's Triad was first described by Widal and subsequently further elucidated by Samter et al.[1-3] The triad is characterized by the presence of nasal polyposis, asthma, and nonsteroidal anti-inflammatory drug (NSAID) intolerance. Most patients also have hyperplastic eosinophilic sinusitis. With movement away from the use of eponyms, this clinical entity is now called aspirin exacerbated respiratory disease (AERD) and is described as the quatrad of asthma, eosinophilic rhinosinusitis, nasal polyposis, and the onset of respiratory reactions after the ingestion of aspirin.[4] AERD has also been described as "non-allergic hypersensitivity reaction."[5]

AERD patients often present as a more severe and treatment-resistant subgroup of asthma and/or chronic rhinosinusitis with nasal polyposis (CRSwNP). AERD patients typically present in their late 20s or 30s and are often significantly affected by their nasal symtoms.[6-8] These patients often require endoscopic sinus surgery for the management of their polyps; polypoid growth is more likely to recur early after surgery and require multiple revision surgeries.[9-11] Topical steroids are utilized almost universally in this patient population, although may be of limited benefit.[12] Although systemic steroids are often beneficial in the short term, both significant long- and short-term side effects limit their usage. ASA desensitization has been shown to be beneficial for many AERD patients; however, side effects, availability, and possible complications prevent this from being a widely utilized treatment.[13]

[1]Division of Otolaryngology-Head and Neck Surgery, McMaster University, Hamilton, Canada
[2]Department of Otolaryngology-Head and Neck Surgery, University of Toronto, Toronto, Canada
[3]Department of Otolaryngology-Head and Neck Surgery, Western University, London, Canada

**Corresponding Author:**
Smriti Nayan, MD, Division of Otolaryngology-Head and Neck Surgery
McMaster University, 1280 Main Street West, 3V1 Clinic, L8S 4L8, 905-802-5412, Canada.
Email: smriti.nayan@medportal.ca

The pathophysiologic mechanisms underlying acetylsalicylic acid (ASA) intolerance have been partially elucidated in the past decade.[14,15] It has been determined that the aspirin intolerance seen in AERD patients is not due to an IgE-mediated reaction, but rather related to the abnormal metabolism of arachidonic acid resulting in an imbalance in the production of leukotrienes and prostaglandins.[15,16] Non-acetylated salicylates, such as those within foods, have been shown to inhibit COX-2 gene expression[17] selectively, which is known to be down-regulated in the nasal polyps of patients with AERD,[17,18] and as such, it follows that these patients may be more likely to react to dietary salicylates.

Clinically, there are an increasing number of studies, including a large meta-analysis showing that patients with mild-to-moderate AERD tolerate selective COX-2 inhibitors.[19] However, there are also reported allergic reactions in patients with AERD who use selective COX-2 inhibitors and oral provocation testing is recommended prior to initiating the medication.[20,21] It is believed that the reason for the variable effects seen with studies examining the mechanism of action of salicylates stems from different experimental parameters involving active inflammatory state and arachidonic acid levels. Furthermore, although it has been shown that non-acetylated salicylates result in preferential COX-2 inhibition, there have also been studies showing paradoxical induction and stimulation of the system.[22]

Links between dietary salicylates and asthma have been determined based on studies of aspirin in patients with asthma.[14] Firm evidence though is lacking with regards to the link between dietary salicylates and nasal symptoms.

There are several publications evaluating the quantities of dietary salicylates found in foods.[23-29] A Scottish systematic review by Wood et al in 2011 demonstrated that the intake of dietary salicylates for men and women, respectively, was 4.42 mg and 3.16 mg per day.[30] This study also helped identify salicylate-rich foods and those low in salicylate.[30] Many fruits contain various amounts of salicylate—especially dried fruits and berries. Herbs and spices are also relatively high sources of dietary salicylates. Adherence to a low salicylate diet may be difficult for some due to the relative exclusion of many fruits, herbs, and spices. Conversely, eggs, grains, legumes, and meats, including fish, are generally considered to be devoid of significant amounts of salicylates. Most alcoholic beverages are a rich source of dietary salicylates; however, gin, vodka, whiskey, and brandy do not contain significant amounts.[30,31] Notably, some of the dietary salicylate level data presented are somewhat inconsistent. This is likely due to variations in food production techniques and geographic origin.[31,32]

To investigate the relationship between diet and respiratory symptoms in patients with AERD, a randomized crossover, blinded pilot study was designed to evaluate the efficacy of a low salicylate diet versus a regular diet. The primary outcome was to determine the feasibility of the study design. The secondary outcome was the effectiveness of the diet by 5 different outcome measure tools.



**Figure 1.** Study design crossover design with 2 assignments.

## Methods

A 12-week, randomized, single-blind, crossover pilot study was designed and McMaster Institutional Research Ethics Board approval was obtained. Six weeks were spent adhering to either a low salicylate diet or regular diet, and a second block of 6 weeks was spent on the other diet. Patients remained on their regular asthma medications, which included combinations of budesonide, ciclesonide, fluticasone, or salbutamol. Patients also continued their topical nasal steroid regimen (nasal steroid spray twice a day and nasal saline irrigations or nasal saline rinse with 1 mg ampule of budesonide once daily or twice daily) (**Figure 1**). There were no other adjunctive medical therapies during the study period. Consecutive adult patients (>16 years old) were seen at the McMaster University Otolaryngology/Head and Neck Surgery clinic and provided informed consent for this study.

Patients with AERD were included based on clinical diagnosis of bronchial asthma, endoscopically confirmed nasal polyposis and self-reported sensitivity (respiratory reaction) to ASA ± other NSAIDs. Patients were excluded if they had undergone endoscopic sinus surgery within the past 6 months or had a course of oral or intravenous steroids within the past 3 months. Patients were also excluded if they had significant mucocele formation. Twenty-two consecutive patients were assessed for eligibility for the study. Eight of these patients did not meet the inclusion criteria: 6 patients had recent surgery, 1 patient was pediatric, and 1 had a sino-nasal mucocele. The 14 remaining patients were appropriate for study enrollment (**Figure 2**).

Patients were randomized to begin either with the low salicylate diet or to continue on their regular diet for 6 weeks, using an online randomization tool.[20] Information packages (containing the salicylate contents of each food, a detailed list of high salicylate foods to be avoided, and a cookbook with examples of recipes were provided to the patients).[22,30] These were compiled from the available literature of salicylate containing foods. During the low salicylate diet, patients were instructed to avoid foods with high (>0.5 mg/portion) salicylate content and consume foods with low (0.01-0.09 mg/portion) salicylate content.[23]
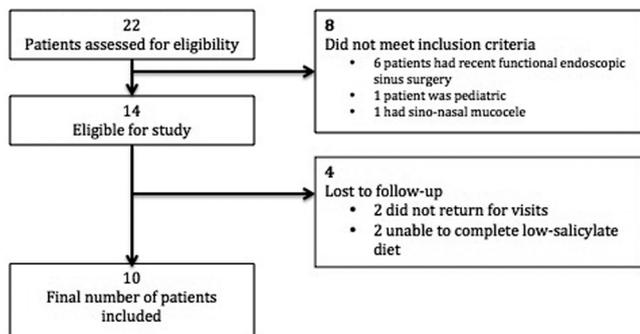
**Figure 2.** Patient allocation.

Patients who were randomized to the regular diet were instructed to follow the usual diet they regularly consumed.

Patients filled out symptom questionnaires (Sino-nasal outcome test-22 [SNOT-22], Asthma Control Questionnaire-7 [ACQ-7], and the Nasal sinus symptom score [NSSS]) at 3 time points: baseline, 6 weeks, and 12 weeks. The physician, who was blinded to the randomization, performed an endoscopic evaluation at the 3 time points of the paranasal sinuses and nasal cavities, which was recorded using the Perioperative Sinus Endoscopy (POSE) and Lund-Kennedy Scoring systems (**Figure 1**). Higher scores on these outcome measures indicate greater severity of sino-nasal or asthma symptoms. On the objective scales an increased score can indicate increased volume of nasal polyps/edema, secretions, or synechiae. Study participants also filled out a Likert-based scale upon completion of the low salicylate diet period at the end of the 6-week period to assess compliance to the diet.

## Statistical Analysis

All data were entered into an Excel database and analyzed using StatsDirect (Chesire, UK). Descriptive analysis was carried out, and medians were reported for each variable in each diet. Medians were chosen instead of means because of the small sample size and ordinal nature of the data.

The data from SNOT-22, ACQ-7, NSSS, Lund-Kennedy nasal endoscopy score, and POSE score was compared between diets and the baseline score for each patient. As these data were dependent and nonparametric, it was analyzed with the Wilcoxon signed rank test. A 2-tailed null hypothesis was presumed and statistical significance was considered at .05 levels. Carryover effect was also calculated.

## Results

A total of 10 patients completed the full 12-week study period (**Figure 1**). Four patients were unable to complete the study (2 patients lost to follow-up and 2 patients were noncompliant to the low salicylate diet). The patients who did not complete the study were demographically similar to the ones who did complete the study.

Of the 10 participants who completed the study, there were 9 females and 1 male with the median age of 48.5

(range, 38-74 years). None of the patients were currently smoking, although 3 had previously. Nine of the patients had undergone previous endoscopic surgery, and 2 of the patients had undergone revision sinus surgery twice (median 2 surgeries per patient; range, 1-3). Anecdotal reports from 3 patients also reported complete resolution of hives/urticarial symptoms while on low salicylate diet.

The median scores for each of the outcome measures and the median changes in each score between baseline and low salicylate diet versus baseline and regular diet are outlined in **Table 1**. Aside from the ACQ-7, patients improved in all subjective and objective measures while on the low salicylate diet. The median change in each score demonstrates that those on the low salicylate diet had reduction in their symptom scores to varying degrees.

Wilcoxon rank sum tests were performed using the difference in scores for each patient on each assessment tool. Statistically significant change on all outcome measures was demonstrated except for the ACQ-7 (**Table 2**). Changes between baseline and the end of the low salicylate diet were statistically significant for the SNOT-22 ($P = .0059$), NSSS ($P = .0195$), POSE ($P = .002$), and Lund-Kennedy Endoscopic Score ($P = .0039$). Changes on the asthma severity questionnaire were not significant ($P = .375$). Differences between baseline and the regular diet were not statistically significant for any of the outcome measures (**Table 2**). Intent-to-treat analysis could not be completed due to the nature of the study design and incomplete data for the 4 patients. There was no statistically significant carryover effect on any of the outcome measures except for the POSE measure ($P = .0476$).

Overall, patients who completed the full study were moderately to highly compliant to the diet. Patient's compliance questionnaires were ranked based on the following criteria: patients who had 5 plus foods (with a very high salicylate level), 6 to 9 times over the course of the low salicylate diet were considered noncompliant; patients who had 3 foods, 6 to 9 times or 3 plus foods (with a high salicylate level), 4 to 6 times were considered moderately compliant; patients who had less than 3 foods, 2 to 3 times were considered very compliant. Seven patients were moderately compliant, and the remaining 3 patients were highly compliant. Two patients who were low in compliance dropped out of the study and did not return for scheduled follow-up.

## Discussion

This study is the first to investigate the role of salicylate dietary restriction as an adjunct in the treatment of AERD patients. Both nasal symptoms and objective nasal findings on endoscopy were improved in this small crossover pilot study.

The prevalence of AERD has been reported to range from 10% to 20% in asthmatic patients and 30% to 40% in patients with nasal polyposis.[8,33,34] If oral provocation is used as the basis of diagnosis, up to 21% of patients with asthma would be considered to have a diagnosis of AERD. However if history of nasal polyps, bronchial asthma, and reactions to ASA are utilized as the diagnostic criteria, the

**Table 1.** Median Values in each Outcome Measure between Baseline and Low Salicylate Diet ($_{LS}$) Versus Baseline and Regular Diet ($_R$).

| | Baseline (median) | 6 Week Low Salicylate Diet (median) | LS Diet (median $\Delta_{LS}$) | 6 Week Regular Diet (median) | R Diet (median $\Delta_R$) | Median $\Delta_{LS}$– Median $\Delta_R$ |
|---|---|---|---|---|---|---|
| Sino-nasal outcome test-22 (SNOT-22) | 49 | 25 | −15 | 46 | 3.5 | −18.5 |
| Asthma Control Questionnaire-7 (ACQ-7) | 12 | 11.5 | −3 | −3 | 4 | −7 |
| Nasal Symptom Severity Score (NSSS) | 7.75 | 4.75 | −2.5 | 7.5 | −0.75 | −1.75 |
| Lund-Kennedy | 11.5 | 8 | −3.5 | 10.5 | −0.5 | −3 |
| Perioperative Sinus Endoscopy (POSE) | 28 | 16.5 | −11 | 25.5 | −2.5 | −8.5 |

**Table 2.** Wilcoxon Rank Sum Test Calculations for each Outcome Measure between Baseline and Low Salicylate Diet ($_{LS}$), Baseline, and Regular Diet ($_R$) and Sum Results LS Versus R.

| | Baseline vs LS P Value | Baseline vs R P Value | Sum Results LS vs R P Value |
|---|---|---|---|
| Sino-nasal outcome test-22 (SNOT-22) | .0059 | .5566 | .2571 |
| Asthma Control Questionnaire-7 (ACQ-7) | .375 | .3223 | .5048 |
| Nasal Symptom Severity Score (NSSS) | .0195 | .4258 | .3429 |
| Lund-Kennedy | .0039 | .7422 | .2 |
| Perioperative Sinus Endoscopy (POSE) | .002 | .6953 | .0476 |

percentage of asthmatic patients with AERD falls to 2.7%.[34] For inclusion to our study, it was felt that it would be more clinically relevant to include only those patients with a clinical history consistent with AERD.

Aspirin sensitivity in AERD patients is modulated by abnormalities in both the cylo-oxygenase and lipo-oxygenase pathways and is not due to an IgE mediated reaction.[17,18,28] AERD patients produce less cyclooxygenase-1 (COX-1) and thus have reduced levels of the prostaglandin E2 ($PGE_2$).[35] These patients are believed to be much more sensitive to a reduction in $PGE_2$, with below normal tonic levels, and this, coupled with dysregulated platelet-leukocyte interactions, results in elevated cysteinyl leukotrienes (Cys-LT) levels.[36] Cys-LT results in a severe respiratory reaction upon ingestion due to its effects on smooth muscle stimulation and resultant edema. AERD patients also have both an overproduction of cys-LTs and increased end-organ reactivity to cys-LTs.[4]

Non-acetylated salicylates are found in dietary sources. The pathophysiology through which non-acetylated salicylates inhibit the COX-1 and -2 systems remains controversial. The role of dietary salicylates and their interactions with the COX-2 system in aspirin sensitivity remain incompletely elucidated at this time. The study attempted to evaluate the effect of dietary salicylates. Other sources of salicylate intake (eg toothpaste, skin/hair products) were not assessed during this study as they were less likely to have a significant impact.

AERD can have a significant impact on patient's daily quality of life and usually results in more severe CRSwNP clinical manifestations. The minimal clinical difference for the SNOT-22 score that can be detected by patients is 8.9

points.[21] The median change for the SNOT-22 in the low salicylate diet cohort was a reduction in scores by 15 points versus a reduction in scores by 3.5 points for the regular diet suggesting that a clinical difference in patient symptom scores was present. Aside from the asthma severity questionnaire, the other outcome measures also had statistically significant differences like the SNOT-22. Furthermore, urticarial reactions to dietary salicylates were described in the late 1950s and several other publications followed in the 60s and 70s,[36-40] 3 patients anecdotally reported cessation of previous urticarial reactions during the low salicylate diet phase of this study.

A low salicylate diet is relatively restrictive in multiple ways, and there is a lack of consensus in the published literature regarding the salicylate contents of foods between studies.[14] Mitchell et al recommend that if dietary exclusion is considered, it should be preceded by a diagnostic diet for 6 weeks, followed by re-introduction of food to prove the efficacy of an exclusion of high salicylate foods.

Patients approached to participate in the study were very enthusiastic about this novel treatment option, often stating that they were willing to try anything in order to reduce their current nasal symptoms. Overall, patients who completed the full study were moderately to highly compliant with the diet. Two patients did not complete the full study, finding the low salicylate diet too restrictive. We recognize this as a limitation to using a low salicylate diet as a potential treatment as it does eliminate several different types of foods such as many fruits, herbs, and spices. However, other treatments have similar difficulty with compliance. In

a study conducted by Sweet et al, approximately 30% of patients dropped out of ASA desensitization therapy due to GI intolerance and other side effects.[31] Dropout rates ranging from 15% to 50% have been recorded in similar ASA desensitization studies.[41,42] The salicylate restricted diet may need to be evaluated by a dietician in order to ensure that individuals are not lacking any required nutrients if utilized long term.

This pilot study has some limitations. These include a relatively small sample size and inconsistency in reported salicylate levels of foods. In addition, there was a ''learning'' effect in implementing the diet and learning which foods are low in salicylates. The first limitation was addressed by implementing a crossover design, which is a more ideal study design for the investigation of short-term outcomes of treatments for chronic diseases such as AERD. The crossover study design also allows for each patient to serve as their own control and thus makes this study design more efficient with a smaller sample size.[43] We attempted to address the second limitation by using published systematic reviews to determine which foods are most commonly high in salicylates. Finally, some of the questionnaire results may be subject to response bias as it was not feasible to blind the subjects to their randomized allocation.

Future directions would include doing a larger, multicenter trial to evaluate external validity of these results as well as determine whether the diet continues to have more longterm benefits on the nasal symptoms of these patients.

## Conclusion

This pilot study appears to demonstrate that a low salicylate diet leads to an improvement in nasal symptoms and objective nasal endoscopic evaluation scores. Further study and evaluation is necessary to determine the mechanism of action and confirm the reported benefit in this study.

## Author Contributions

**Doron D. Sommer**, contributions to the conception and design of the work and data acquisition, revising and approving the final version of the published manuscript, responsible for all intellectual content of the manuscript; **Stephanie Hoffbauer**, data acquisition, drafting and final approval of the manuscript, responsible for all intellectual content of the manuscript; **Michael Au**, data acquisition, revising and final approval of the manuscript, responsible for all intellectual content of the manuscript; **Leigh J. Sowerby**, contributions to study design, data acquisition, revising and approving the final version of the manuscript, responsible for all intellectual content of the manuscript; **Michael K. Gupta**, data interpretation, revising and approving the final version of the manuscript, responsible for all intellectual content of the manuscript; **Smriti Nayan**, contributions to study design; acquisition, analysis, and interpretation of data for the work; drafting, revising, and approving the final version of the published manuscript; responsible for all intellectual content of the manuscript.

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