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Review Article

Olfactory outcomes in the management of aspirin exacerbated respiratory disease related chronic rhinosinusitis

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Abstract Patients with aspirin exacerbated respiratory disease (AERD) experience a severe and recalcitrant form of chronic rhinosinusitis with nasal polyposis (CRSwNP) and asthma, which are exacerbated by aspirin/NSAID ingestion. As compared with aspirin-tolerant CRSwNP, patients with AERD experience more severe olfactory dysfunction, which is one of the key contributors to the observed decrease in quality of life (QOL) in this disease. The objective of this paper is to review the published olfactory outcomes observed with various treatment modalities.

Background

Aspirin exacerbated respiratory disease (AERD) is defined as chronic rhinosinusitis with nasal polyposis (CRSwNP) and asthma, which is acutely worsened by aspirin (ASA)/NSAID ingestion. This condition was initially described by Widal et al in 1922 and later coined Samter's Triad after Samter and Beer's publication in 1968.[1,2] The true prevalence of AERD is difficult to ascertain, but is estimated to be 0.3%–0.9% of the population and 7% in patients with asthma.[3]

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Table 1 Studies presented.

Intervention category	Source	Intervention	Study type	Population (*n*)	Olfactory outcome metric	Results[a]
ESS	Mendelsohn et al[7]	ESS	Cohort	50	Patient reported olfactory dysfunction: yes/no	Preop: 46/50 (92%) Postop: 28/47 (59%)[b]
	Young et al[10]	ESS	Case series	11	Visual analog scale range: 0—10	Preop: 9.32 ± 1.38 Postop 24 mo: 6.13 ± 4.33* Postop 36 mo: 8.00 ± 2.83*
ASA	Berges-Gimeno et al[30]	ASA (650 mg Bid)	Cohort	126	Patient reported olfactory dysfunction: interval scale 0—5 0 = complete anosmia 3 = partial smell, majority of time 5 = perfect, continuous sense of smell	Baseline: 0.0[c] Post ASA (6 mo.): 3.0* Post ASA (1 yr.): 3.0*
	Gudziol et al[15]	ASA (300 mg daily)	Cohort	AERD: 16 Control (CRSwNP):15	Sniffin' Sticks TDI Score range: 1—48 Hyposmia <30 and ≥15 ansomia <15	*Baseline* AERD: 19.16 ± 9.52 CRSwNP: 26.80 ± 10.25 *Post ASA (7 mo.)* AERD: 20.66 ± 9.29 CRSwNP: 26.02 ± 10.44
	Walters et al[31]	ASA (40.5—1300 mg daily)	Case series	92	Patient reported olfactory dysfunction: interval scale 0—5 0 = complete anosmia 3 = partial smell, majority of time 5 = perfect, continuous sense of smell	Baseline: 0.66 ± 1.06* Post ASA: 1.74 ± 1.65*
	Świerczyńska-Krępa et al[32]	ASA (624 mg daily)	Cohort; double blinded placebo controlled	AERD + ASA: 8 AERD + Placebo: 7 ATA + ASA: 5 ATA + placebo: 8	Visual analog scale range: 0—10	*Baseline → Post ASA (6 mo.)* AERD-ASA: 10.0 → 6.3* AERD-placebo: 8.0 → 8.4 ATA - ASA: 8.2 → 8.0 ATA - placebo: 6.5 → 8.3
	Ibrahim et al[32]	ASA (325—650 mg Bid)	Case series	111	Patient reported improvement in smell: yes/no	Post ASA improvement: 34/111 (30.6%)
	Sweet et al[33]	ASA 650 mg Bid (average)	Cohort	AERD + Placebo (Control): 42 AERD + discontinued	Patient reported olfactory dysfunction: interval scale 1—5 1 = perfect smell	Change in score at follow-up Control: −0.1 Long term

Table 1 (*continued*)

Intervention category	Source	Intervention	Study type	Population (*n*)	Olfactory outcome metric	Results[a]
				ASA: 30 AERD + ASA long term: 35	5 = complete anosmia	ASA: −1.2* Short term ASA: −1.3* → +0.5 after d/c
	Rozsasi et al[34]	ASA 100 mg vs. ASA 300 mg	Cohort	ASA 100 mg: 7 ASA 300 mg: 7	Sniffin' Sticks odor identification range: 0—12	*Difference*[c] *(12 mo. Post ASA Score - Baseline)* 300 mg: −3* 100 mg: +1
Monoclonal antibodies	Laidlaw et al[35]	Dupilumab	Cohort; double blinded placebo controlled	Control (AERD): 11 Dupilumab: 8	UPSIT + SNOT-22 Smell Subscore	>50% reduction post Dupilumab at 4 mo.* (numerical data not published)
	Philips-Angles et al[36]	Omalizumab	Case series	7	Visual analog scale range: 0—4	Olfactory improvement in 5/7 (71%) at 6 months[b]
	Tiotiu et al[37]	Omalizumab	Case Series	AERD: 9	Visual analog scale range: 0—10	Baseline → Post Omalizumab (6 mo.) 8.67 ± 1.33 → 5.44 ± 2.62*
	Hayashi et al[38]	Omalizumab	Case Series	21	Visual analog scale range: 0—10	Baseline → Post Omalizumab (12 mo.) 8.8 (4.6—10) → 3.0 (0.9—7.4)[c,*]
	Tuttle et al[39]	Mepolizumab	Case series	14	SNOT-22 smell subscore range: 1—5	Baseline → Post Mepolizumab (12 mo.) 4 → 3*
Combination therapy	Havel et al[40]	ESS vs. ESS + ASA (500 mg daily)	Cohort	ESS = 81 ESS + ASA = 65	Patient reported olfactory dysfunction: interval scale 1—4 1 = no symptoms 4 = severe symptoms daily	*ESS* Preop: 3.72 Postop (1 yr): 3.52 Long term (min 18 mo.): 3.55 *ESS + ASA* Preop: 3.80 Postop (1 yr): 2.56* Long term (min 18 mo.): 2.94*
	Cho et al[41]	ESS + ASA (325—650 mg BID)	Case Series	ESS + ASA = 21	SNOT-22 smell subscore range: 1-5	Baseline Preop: 4.1 ± 1.3 Postop (1 mo.): 1.2 ± 0.9*

(*continued on next page*)

Table 1 (*continued*)

Intervention category	Source	Intervention	Study type	Population (*n*)	Olfactory outcome metric	Results[a]
	Fruth et al[42]	ESS + low dose ASA (100mg) vs. ESS + placebo	Cohort; Double Blinded Placebo Controlled	ESS + ASA: 18 ESS + placebo: 13	*Sniffin' Sticks Odor Identification* Range: 0–8 Score = mean sum of correctly identified items on each side	Post ASA (6 mo.): 1.9 ± 0.4 Post ASA (24 mo.): 1.4 ± 0.5 *Difference (36 mo. Postop Score - Preop)* Placebo: 0.2 ASA: 1.9

*$p < .05$.

ASA: aspirin desensitization therapy; TDI: threshold, discrimination, identification score; CRSwNP: chronic rhinosinusitis with nasal polyposis; SNOT-22: Sinonasal Outcome Test-22; ATA: aspirin tolerant asthma.

[a] Mean, unless otherwise noted.

[b] Statistical significance not reported.

[c] Median (interquartile range).

Table 2 Summary of studies presented.

Intervention	Numbers of studies	Studies with improvement in olfactory measurement (# of studies/total)	Statistically significant benefit (# of studies/total)
ESS	2	2/2	1/2
ASA	7	6/7	5/7
Monoclonal antibodies	5	5/5	4/5
ESS + ASA	3	3/3	2/3[a]

[a] Study by Fruth et al[42] did not demonstrate statistically significant benefit but utilized 100 mg ASA daily, lower than the currently recommended 325–1300 mg daily dosage.

Patients with AERD experience an increase in upper and lower airway reactivity following exposure to Cox-1 inhibitors, i.e. ASA or nonsteroidal anti-inflammatory drugs (NSAIDs). Symptoms may manifest as early as 30 minutes after ingestion, with increased nasal congestion, rhinorrhea, shortness of breath, or wheezing. Extra-pulmonary cutaneous and gastrointestinal symptoms have also been documented in a subset of patients.[4,5] Diagnosis is established with ASA challenge testing. Over time, patients develop nasal polyposis, nasal obstruction, and hyposmia.

The sinonasal symptoms associated with AERD are often severe and prompt patients to seek intervention. As compared to their counterparts with ASA-tolerant chronic rhinosinusitis, patients with AERD tend to have recalcitrant disease, requiring more frequent and revision sinus surgery with higher rates of healthcare utilization.[6–8] Unfortunately, these patients also have poorer outcomes after endoscopic sinus surgery (ESS) as measured by symptom metrics and endoscopic findings.[9,10] Nevertheless, ESS has still proven to be a critical treatment modality with sustained clinical improvement after long term follow-up, despite the higher likelihood for revision surgery.[11,12]

AERD and olfaction

Olfactory dysfunction is a widely recognized component of chronic rhinosinusitis (CRS) with 78% of patients suffering from diminished or absent sense of smell.[13] This impairment is thought to occur due to both obstruction of the olfactory cleft secondary to edema and nasal polyposis as well as direct inflammation of the olfactory mucosa.[14] Gudziol et al[15] demonstrated that patients with AERD have more severe hyposmia as compared to patients with ASA-tolerant CRSwNP.[15,16] The pathophysiology of this difference in olfaction has not been fully elucidated. While many CRSwNP patients have obstructive edema and polyposis, the increased hyposmia in patients with AERD as compared with those with similarly severe CRSwNP suggests the possibility of unique inflammatory changes to the olfactory mucosa and neurons that are not seen in other patients.[15]

Quality of life (QOL) surveys from patients with AERD indicate that hyposmia in particular is a major driver of QOL loss.[17] Patients with AERD report high rates of frustration, fatigue, irritability and depression.[17] Chronic nasal

symptoms and decreased sense of smell contribute most to patients' decrease in QOL.[17] Although olfaction is included in most metrics of sinonasal disease, it is not necessarily correlated with improvements in other symptom domains, such as nasal obstruction or rhinorrhea. Patients with AERD are also at higher risk of impaired eating related QOL because of the interplay between olfactory dysfunction and taste.[18] Despite the known effect of hyposmia on patients' quality of life, many publications do not explicitly track olfactory outcomes following treatment. This paper aims to review the available data on the effects of various treatment modalities on olfaction in patients with AERD.

Methods of measurement

Before evaluating the olfactory outcomes, it is important to understand the various metrics that are used in clinical practice and research. The available diagnostic tools can be divided into two categories: subjective patient reported outcome metrics (PROMs) and objective tests of the olfactory system.

Patient reported outcome measures

The most common PROM is a component of the Sinonasal Outcome Test-22 (SNOT-22), which contains a question asking patients to rate the severity of their limitation in smell and taste. This metric uses a Likert scale from 0 to 5 where 0 is "no problem" and 5 is that the "problem is as bad as it can be." The SNOT-22 questionnaire has been used extensively to measure outcomes in chronic rhinosinusitis. However, there are 15 different patient reported outcome metrics that have been validated for use in CRS.[19] Visual analog scales are also used as standalone questions in some studies or as a component of a validated metric, such as the Rhinosinusitis Task Force symptom score.[19] Some studies dichotomize this question into normal olfaction versus impaired sense of smell, while others use a categorical variable classifying olfaction as normal, diminished, or absent.

While PROMs are much easier to administer, it is important to understand their limitations. An interesting study by Landis et al demonstrates that healthy subjects are unable to accurately self-report their sense of smell. However, the accuracy of this self-assessment improves after undergoing olfactory testing, forcing them to pay conscious attention to their sense of smell.[20] Fortunately, in patients with sinonasal disease, the sensitivity of self-reported olfaction impairment is much higher, greater than 90% in multiple studies.[21,22] However, the specificity of this question is lower, such that patients with sinonasal disease overstate their diminished sense of smell.[21,22] Interestingly, one's perception of their sense of smell is closely correlated with nasal airflow,[20] which may explain CRS patients' tendency to overestimate their extent of olfactory impairment.

Objective olfactory assessments

The University of Pennsylvania Smell Identification Test (UPSIT) assesses an individual's ability to identify 40 odors and has a high retest reliability, $r = 0.9$.[23] Scores range from 0 to 40, corresponding to the number of correctly identified odors. The advantage of the forced-choice nature of this assessment allows for potential detection of malingering, which is suggested by a score <10, which would be achieved by someone with complete anosmia that is randomly guessing.[24]

In an effort to make olfactory testing more widely available and easier to use, two modifications of the UPSIT were developed, known as the Connecticut Chemosensory Clinical Research Center (CCCRC) test and the Cross-Cultural Smell Identification Test (CC-SIT). The CCCRC test assesses odor identification of 10 scents and olfactory threshold; $r = 0.77$.[25] The CC-SIT was designed as the most rapid test and assesses only odor identification of 12 scents with a retest reliability $r = 0.71$.[26]

"Sniffin' Sticks" is an olfactory test that has also been widely used and validated in patients with CRS.[27] Sniffin Sticks can be used to test olfactory thresholds, odor discrimination, or odor identification. Often, a combination assessment of these three domains is used, called the TDI score (range: 1–48). A TDI score ≤ 15 signifies anosmia, ≤ 30 signifies hyposmia, and >30 is seen in normal participants.[28,29] The retest reliability for the composite assessment is $r = 0.72$.[29]

Outcomes

Endoscopic sinus surgery

Of the many studies that evaluate ESS in patients with AERD (Table 1), only two report olfactory outcomes of ESS without associated ASA desensitization — both utilizing PROMs. Mendelsohn et al demonstrate a significant decrease in olfactory dysfunction following ESS: 92% preoperatively compared with 59% postoperatively.[7] In a case series, Young et al demonstrate a decrease in patient reported olfactory dysfunction 24 months after ESS, but this trended back towards preoperative anosmia levels 3 years postoperatively.[10]

Aspirin desensitization therapy

All seven studies that evaluate olfactory outcomes following ASA desensitization demonstrated improvements in patient reported and objective assessments of olfactory function with six out of seven studies reporting statistical significance (Table 2). The dosage of ASA used ranged from 40.5 mg daily to 650 mg BID. One study by Rozsasi et al[34] directly compared two dosages of ASA (100 vs. 300 mg) and demonstrated a significant improvement in olfaction only in the group receiving 300 mg daily.[34] In one of the earliest landmark studies, Sweet et al studied outcomes in individuals who were on long term ASA therapy and those who discontinued therapy for a variety of reasons. Patient reported outcomes demonstrate statistically significant improvement while on ASA with a subsequent worsening of symptoms after discontinuation.[33]

Biologic agents — monoclonal antibodies

Three biologic agents are currently used in the management of AERD. Omalizumab, initially developed for the

management of severe asthma has also been demonstrated to improve desensitization rates in those who previously failed ASA therapy due to adverse reaction. Hayashi et al demonstrate a statistically significant decrease in patient reported olfactory dysfunction after 1 year of treatment with omalizumab (8.8 → 3.0).[38] Two additional case series also demonstrate improvement in patient reported olfaction, which did not reach statistical significance.[36,37]

Mepolizumab, an anti-IL-5 human monoclonal antibody, was studied in 14 patients with AERD. Patients reported a statistically significant improvement in the smell/taste subscore of the SNOT-22 questionnaire (4 → 3) following treatment.[39]

Most recently, Liadlaw et al published results from a subset of patients with AERD participating in a larger trial evaluating the effectiveness of Dupilumab, an anti-IL-4 and IL-13 human monoclonal antibody, in the management of CRSwNP. Patients exhibited a >50% improvement in olfactory dysfunction as measured by the UPSIT and SNOT-22 assessments ($p < .005$).[35]

Combination therapy: ESS + ASA

Three studies report olfactory outcomes following combination ESS with subsequent ASA desensitization (500 mg daily). Havel et al demonstrated statistically significant reductions in patient reported olfactory dysfunction after ESS and ASA desensitization. The same effect was not observed in the control group, who received ESS without subsequent ASA desensitization.[40] Similar outcomes are noted in a case series by Cho et al with a statistically significant decrease in SNOT-22 smell subscore postoperatively that is maintained with ASA desensitization.[41] Fruth et al performed a double blinded placebo-controlled cohort study comparing ESS + low dose ASA desensitization (100 mg daily) to ESS + placebo. While the experimental group exhibited an improvement in odor identification of Sniffin' Sticks, statistical significance was not achieved.[42]

Conclusion

Olfactory dysfunction has a major negative impact on the QOL of patients with AERD. In patients with AERD, improvements in other sinonasal symptoms may not be correlated with improvement in sense of smell. There is considerable evidence that each of the reviewed therapies (ESS, ASA desensitization, and monoclonal antibodies) improves olfaction in patients with AERD. It is difficult to directly compare the results of these studies because of heterogeneity in patient populations and treatment algorithms, which make performing a meta-analysis challenging. The available data is suggestive of improved long term olfactory outcomes with multi-modality therapy, specifically ESS + ASA desensitization. To the authors' knowledge there are no studies to date that investigate synergistic effects and olfactory outcomes of monoclonal antibodies with aspirin desensitization or surgical therapy. Additional research using objective outcome measures is needed to demonstrate which therapies offer the most improvement in olfactory dysfunction, a facet of AERD that significantly contributes to worsened QOL. Clinicians and researchers should pay specific attention to olfactory symptoms in patients with AERD.

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Declaration of competing interest

None.

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