

Aspirin-exacerbated respiratory disease: longitudinal assessment of a large cohort and implications of diagnostic delay

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Background: Aspirin-exacerbated respiratory disease (AERD) refers to the combination of asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and acute respiratory tract reactions to ingestion of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). There have been no in the literature investigating diagnostic delay in AERD. We aimed to investigate whether delay of diagnosis of AERD is associated with poorer clinical outcomes as well as to characterize the role of specialty evaluation in diagnosis.

Methods: We conducted a retrospective observational study of 254 subjects with incident AERD diagnoses between 2009 and 2016 among Kaiser Permanente Northern California (KPNC) members. Descriptive and bivariate statistics were employed to analyze clinical characteristics and outcomes of AERD subjects with and without delay in diagnosis (defined as 1 year or greater from symptom onset to diagnosis).

Results: Of the 254 patients in the AERD cohort, 24.4% had a delayed diagnosis. Patients with allergies were significantly less likely to have a delay in diagnosis ($p < 0.01$). Pa-

tients with a delay in diagnosis were more likely to have 2 or more courses of systemic steroids ($p = 0.04$). Allergists, otolaryngologists, and primary care physicians diagnosed 56%, 36%, and 8% of patients, respectively. There was no association between provider specialty at time of diagnosis and delay in diagnosis ($p = 0.22$).

Conclusion: A substantial proportion of AERD patients have a diagnostic delay. Patients with allergies have a lower risk for this delay. This study is the first to describe diagnostic delay in AERD patients. © 2020 ARS-AAOA, LLC.

Key Words:

aspirin-sensitivity; aspirin-triad; asthma; chronic rhinosinusitis; diagnostic delay; Samter's; aspirin-exacerbated respiratory disease

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Aspirin-exacerbated respiratory disease (AERD) refers to the combination of asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and acute upper and lower respiratory tract reactions to ingestion of aspirin (acetylsalicylic acid [ASA]) or other cyclooxygenase-1

(COX-1)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs).¹ AERD affects 0.3% to 0.9% of the general population and approximately 7% of asthmatics.² The prevalence of patients with ASA hypersensitivity is approximately 1% in the general population and increases to 5% to 10% in adult patients with asthma and 30% to 40% in patients with both asthma and nasal polyposis.³⁻⁶

In the setting of AERD, CRSwNP is very challenging to manage and represents one of the most recalcitrant forms of chronic rhinosinusitis (CRS). Nasal polyp burden is more severe, and nasal polyps are more likely to be refractory to both medical and surgical treatment.⁷⁻¹¹ Even with surgery, 37% of patients require revision surgery at 5 years and 89% at 10 years.¹² Similarly, lower airway disease is difficult to manage because many patients have more severe forms of asthma that often require multiple courses of systemic therapy and multiple office and hospital visits. ASA desensitization therapy has emerged as an adjunctive therapy in these

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challenging cases, with most trials demonstrating clinical improvement.¹³

Recognition and prompt diagnosis of AERD is critical to the successful management of these patients. Accurate and early diagnosis can lead to initiation of appropriate medical and surgical therapies. However, AERD often goes unrecognized because of disease-specific and healthcare system-specific factors. The disease-specific factors which lead to the underdiagnosis of AERD include the time course of disease and the fact that patients may not be aware of symptoms induced by aspirin. AERD typically is diagnosed in adulthood. The majority of patients first develop CRS, followed by asthma, and then aspirin or NSAID sensitivity over the course of years that is slowly progressive.¹⁴ Furthermore, patients may only have mild symptoms induced by aspirin. In the European Network of Aspirin-Induced Asthma, 18% of participants were unaware of aspirin sensitivity before undergoing blinded aspirin provocation tests.¹⁵ The healthcare system-related factors that contribute to AERD underdiagnosis include low clinical awareness of this syndrome among healthcare professionals and its demand for multispecialty management.¹⁵ Management of AERD often involves the otolaryngologist, allergist, and pulmonologist, and recognition can occur at all levels of care.

There are few large epidemiologic studies on AERD patients.^{7,14,16} Large longitudinal studies allow us to characterize disease manifestation and clinical progression, especially for chronic conditions. Furthermore, there have been very few studies in the literature investigating the diagnostic challenges of AERD. This handful of studies has focused on the dilemma of diagnosing aspirin sensitivity based on patient report versus a formal oral aspirin challenge.^{3,17,18} We hypothesize that diagnostic delay in AERD can contribute to poor clinical outcomes. The inability to offer appropriate treatment to AERD patients can lead to nasal polyp recurrence and the need for additional surgeries. In a series of 15 patients, 80% of patients who did not undergo aspirin desensitization required revision surgery.¹⁰ Other studies in otolaryngology on oropharyngeal squamous cell carcinoma,^{19,20} oral cavity cancer,²¹ and laryngeal lesions²² have also shown that diagnostic delay can lead to poor clinical outcomes. We aimed to describe a large cohort of AERD patients to further understand disease course, identify whether there is clinical diagnostic delay, and investigate whether diagnostic patterns contribute to clinical outcomes.

Patients and methods

Patient selection

A retrospective observational study was conducted within Kaiser Permanente Northern California (KPNC), a large integrated healthcare system. The cohort was composed of patients diagnosed with AERD from January 1, 2009 to December 31, 2016. Subjects were identified through

the electronic medical record by searching for specific International Classification of Diseases, 9th edition (ICD-9) or International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes specifying “Aspirin-Exacerbated Respiratory Disease,” “Aspirin Sensitivity,” and “Hx of Aspirin Sensitive Asthma w Nasal Polyp.” This was performed in combination with chart review of allergy documentation for aspirin or NSAID allergy, which is similar to the protocol described by Cahill et al.²³ Patients were excluded if they were less than 18 years old at the time of AERD diagnosis, if they had a previous diagnosis of AERD (confirmed via chart review), if they had had KPNC membership for less than 2 years prior to diagnosis of AERD, or if they had less than 1 year of follow-up after diagnosis of AERD.

After diagnosis of AERD at our institution, patients receive an allergy and otolaryngology evaluation. If patients have symptoms affecting quality of life despite medical therapies, then surgery is discussed with the otolaryngologist. All patients are referred to an allergist for aspirin desensitization. This cohort includes patients at multiple institutions in our healthcare system across Northern California, so there may be some interinstitutional variability.

Evaluation of diagnostic delay and data collection

We defined diagnostic delay as AERD diagnosis occurring 1 year or later from symptom onset. Representative diagnostic timeline scenarios for patients with and without diagnostic delay are illustrated in Figure 1. Patients with an AERD diagnosis date later than 1 year from the AERD symptom onset date (or after the index date) were categorized into the delayed diagnosis group. Key definitions for how we determined date of symptom onset, delay in diagnosis, and dates of clinical outcome follow-up are described in Table 1. Data obtained from clinical chart review included date of symptom onset for CRSwNP, asthma, and ASA/NSAID intolerance, provider specialty at time of symptom onset, and method of AERD diagnosis (history and physical exam, or aspirin provocation/challenge). The number of sinus surgeries, disease-related emergency room (ER) visits, disease-related doctor's office visits (DOV), disease-related hospital admissions, computed tomography (CT) sinus Lund-Mackay radiographic scores (from score recorded closest to the date of symptom onset and score recorded closest to the index date), and pulmonary function testing (test recorded closest to the date of symptom onset and test recorded closest to the index date) were also obtained through clinical chart review. For pulmonary function testing, we identified the forced expiratory volume at 1 second (FEV1) and FEV1/forced vital capacity (FEV1/FVC) as parameters of interest. To help account for the confounding effect of disease severity, proxies for disease severity (CT sinus Lund-Mackay Score and FEV1/FVC) were measured at the symptom onset baseline and at index. All outcome variables were measured in the year following the index date to also help account for confounding.

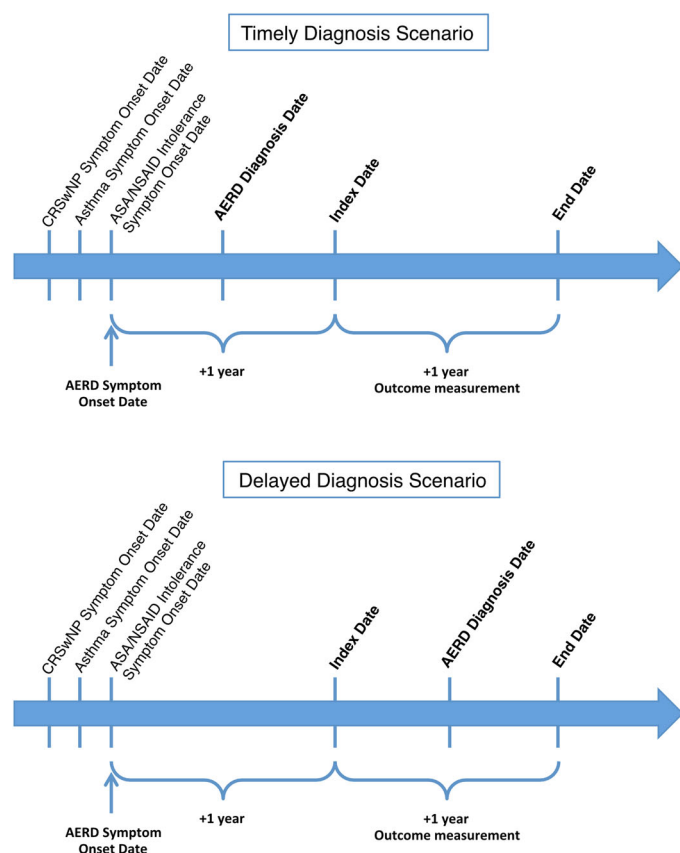


FIGURE 1. Timelines for those with delay in diagnosis (time from symptom onset to diagnosis ≥ 1 year) and those without delay in diagnosis (<1 year). Patients with an AERD diagnosis date greater than 1 year after AERD symptom onset date (or after index date) were put into the delayed diagnosis group. AERD = aspirin-exacerbated respiratory disease.

Data electronically extracted from the medical record included demographic variables (age, sex, race/ethnicity), social habits (smoking, alcohol), medical comorbidities (allergies, obesity, obstructive sleep apnea, gastroesophageal reflux disease [GERD], chronic obstructive pulmonary disease [COPD], diabetes mellitus), date of first specialty visit following AERD symptom onset (with otolaryngologist, allergist, pulmonologist), date of first specialty visit following AERD diagnosis (with otolaryngologist, allergist, pulmonologist), number of courses of systemic corticosteroids within 1 year after index date, and number of courses of systemic antibiotics within 1 year after index date. GERD (530.81, K21.x), allergies (477.x, J30.1, J30.2, J30.5, J30.8x, J30.9), COPD (491.x, 491.xx, 492.x, 506.4, 494.x, 506.x, J40, J41.x, J42, J43.x, J44.x, J47), and sleep apnea (327.23, G47.33) were defined by ICD-9 and ICD-10 codes. If the subject had a documented code for these comorbidities within 2 years of symptom onset, we considered the subject to have the comorbidity. Obesity was defined by calculating the subject's body mass index (BMI) using the subject's height and weight measurements closest to the index date. If BMI was above 30 then the subject was considered obese. Presence of diabetes was considered if the subject was on the diabetes registry prior to the index date.

Statistical analysis

The average, median, and interquartile range (IQR) of time from symptom onset to diagnosis of AERD and proportion of individuals with delay in diagnosis were calculated. We also measured proportions of provider specialties that saw

TABLE 1. Variable descriptions

Variable	Definition
CRSwNP symptom onset date	The earliest date that the patient had (1) 2 of the following symptoms (nasal obstruction/congestion, nasal drainage/discharge, decreased sense of smell, facial pain/pressure) AND (2) objective evidence of sinonasal inflammation as documented by radiographic imaging (ie, CT) or nasal exam or endoscopy.
Asthma symptom onset date	The earliest date that the patient had (1) 2 of the following symptoms (difficulty breathing, chest tightness, cough, wheezing) WITH symptoms occurring or worse at night, with exercise, viral infection, allergen exposure, changes in weather, hard laughing or crying, or stress AND (2) objective evidence of partially reversible airflow obstruction as documented on pulmonary functional testing: diurnal variation in PEF of more than 20% over 1–2 weeks, increase of at least 12% and 200 mL in FEV1 after bronchodilator use, or reduced FEV1/FVC ratio using spirometry.
ASA/NSAID intolerance symptom onset date	The earliest date that the patient demonstrated nasal or pulmonary symptoms to ASA or NSAID medication or the date at which ASA or NSAID medication was input as an “allergy” on chart.
AERD symptom onset date	The latest of the 3 dates: “CRSwNP Symptom Onset Date”, “Asthma Symptom Onset Date”, and “ASA/NSAID Intolerance Symptom Onset Date.”
Index date	AERD symptom onset date + 1 year
End follow-up date	Index date + 1 year
AERD diagnosis date	Date at which diagnosis of AERD was made.
Delay in diagnosis	To separate patients into 2 cohorts: those with delay in diagnosis (time from symptom onset to diagnosis ≥ 1 year) and those without delay in diagnosis (<1 year).

AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid; CRSwNP = chronic rhinosinusitis with nasal polyposis; CT = computed tomography; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; NSAID = nonsteroidal anti-inflammatory drug; PEF = peak expiratory flow.

patients at time of symptom onset and diagnosis as well as the average (median, IQR) time to specialist (allergist, otolaryngologist, pulmonologist) visit. Subjects were stratified by whether or not they had a delay in diagnosis to compare demographic and clinical characteristics between groups. As age was found to be normally distributed, we performed the Student *t* test to compare mean age (in years) between patients with AERD diagnostic delay to those without. Bivariate comparisons on frequencies of categorical demographic characteristics (sex, race), clinical characteristics (obesity, GERD, COPD, sleep apnea, diabetes, smoking tobacco use, alcohol use, allergies), and clinical outcome variables were made using the chi-square and Fisher's exact tests. A *p* value of 0.05 was considered statistically significant.

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). This study was approved by the Kaiser Foundation Research Institute's Institutional Review Board with waiver of consent. Funding for this study was provided by a grant from the KPNC Community Benefit Program.

Results

Our review yielded 254 patients with AERD who met final inclusion criteria. Table 2 displays the demographic information and comorbidities for the AERD cohort. The mean age of the cohort was 48.7 years and a slight majority of patients were female (58.3%). The cohort was predominantly comprised of white non-Hispanics (59.1%).

Sixty-two patients (24.4%) in our cohort had a diagnostic delay. Table 2 displays the differences in delay in diagnosis for each demographic and comorbidity variable. Patients with allergies were less likely to have a delay in diagnosis ($p < 0.01$). There were no other statistically significant differences between the cohort with diagnostic delay and the cohort without diagnostic delay with regard to demographics or comorbidities.

Figure 2 illustrates the distribution of the number of days to diagnosis, calculated as the time in days from the date of symptom onset to the date of AERD diagnosis. The Shapiro-Wilk test of normality revealed a non-normal distribution ($p < 0.01$) of days to diagnosis. The median number of days from symptom onset to diagnostic date was 0, with an upper quartile of 355 days, and a maximum of 3588 days.

Table 3 highlights relevant clinical outcomes for the AERD cohort. Patients with a delay in diagnosis were more likely to have 2 or more courses of systemic steroids (46.8% vs 32.3%, $p = 0.04$). We did not find a statistically significant difference in any other clinical outcome that we examined between the 2 groups.

Most patients were diagnosed by history and physical exam (248, 97.6%), whereas 6 (2.4%) patients were diagnosed by aspirin challenge. At the time of symptom onset, 83 (32.7%) patients were seen by allergy, 74 (29.1%) were seen by otolaryngology, and 97 (38.2%)

were seen by primary care medicine/pulmonology/other (Table 4). At the time of diagnosis, 141 (55.5%) patients were seen by allergy, 92 (36.2%) were seen by otolaryngology, and 21 (8.3%) were seen by primary care medicine/pulmonology/other (Fig. 3). There was no significant difference between provider specialty at time of diagnosis and delay in diagnosis ($p = 0.22$); however, there was a statistically significant association between provider specialty at time of symptom onset and delay in diagnosis ($p < 0.01$).

The specialty department of first visit after symptom onset was allergy in 204 (84%) patients, otolaryngology in 18 (7.4%) patients, and pulmonology in 21 (8.6%) patients. The times (median [Q1, Q3]) between symptom onset and provider visit are given in Figure 4. The specialty department of first visit after diagnosis was allergy in 217 (90%) patients, otolaryngology in 12 (5%) patients, and pulmonology in 12 (5%) patients.

Discussion

Epidemiologic studies on AERD

Epidemiologic studies help describe the clinical course of a disease and provide information on disease prevalence and treatment outcomes. This is important in AERD because few large studies exist that describe demographic information and clinical outcomes. There has been wide variability in the reporting of the prevalence of AERD. A 2004 meta-analysis demonstrated prevalence rates ranging from 21% among asthmatic adults based on oral aspirin challenge and 2.7% based on patients' histories.²⁴ A more recent systematic review in 2015 estimated the overall prevalence of AERD in asthmatic patients to be 7.15%.²⁵ This study highlighted recent AERD cohorts and their estimated study prevalence.²⁵ Table 5 displays demographic and outcome data for other large AERD cohorts. There is some variation in the percentage of female patients, with 2 of the studies having a significantly higher proportion of female patients with AERD compared to this study's cohort (58.3%).

Over 70% (70.5%) of patients in the cohort reported never being exposed to tobacco smoke (Table 2). This contrasts with previous reports, which have associated active or passive smoking with the onset of AERD.²⁶ Chang et al.²⁷ reported that active smoking and childhood environmental tobacco smoke exposure was associated with increased odds of developing AERD.

Delay in diagnosis

This is the first study in the literature to investigate diagnostic delay for AERD. In our study, 24.4% of patients had a diagnostic delay of 1 year or more from symptom onset. Overall, there were no significant differences in the patients without diagnostic delay in terms of demographics or comorbidities except for the presence of allergies. This may be because patients with allergies presumably see specialists more frequently. Allergists made most diagnoses, followed

TABLE 2. Demographic characteristics and comorbidities of study population of AERD patients*

Characteristic at baseline	Total (n = 254)	Delay in diagnosis		χ^2 p
		No (n = 192)	Yes (n = 62)	
Age (years), mean $\pm$ SD	48.7 $\pm$ 13.4	48.6 $\pm$ 13.6	49.3 $\pm$ 12.7	0.73 ^a
Sex, n (%)				0.08
Female	148 (58.3)	106 (55.2)	42 (67.7)	
Male	106 (41.7)	86 (44.8)	20 (32.3)	
Race, n (%)				0.48
Asian	36 (14.2)	28 (14.6)	8 (12.9)	
Black	25 (9.8)	16 (8.3)	9 (14.5)	
Hispanic	30 (11.8)	21 (10.9)	9 (14.5)	
White	150 (59.1)	118 (61.5)	32 (51.6)	
Other	13 (5.1)	9 (4.7)	4 (6.5)	
Obesity, n (%)	72 (28.4)	50 (26.0)	22 (35.5)	0.15
GERD, n (%)	74 (29.1)	53 (27.6)	21 (33.9)	0.35
Allergies, n (%)	175 (68.9)	143 (74.5)	32 (51.6)	<0.01
Alcohol use, n (%)				0.58 ^b
No	108 (42.5)	79 (41.1)	29 (46.8)	
Unknown	1 (0.4)	1 (0.5)	0 (0.0)	
Not asked	11 (4.3)	10 (5.2)	1 (1.6)	
Yes	134 (52.8)	102 (53.1)	32 (51.6)	
Smoking tobacco use, n (%)				0.22 ^b
Current	8 (3.2)	7 (3.6)	1 (1.6)	
Never	179 (70.5)	129 (67.2)	50 (80.6)	
Passive	1 (0.4)	1 (0.5)	0 (0.0)	
Former	66 (26.0)	55 (28.6)	11 (17.7)	
Diabetes, n (%)	17 (6.7)	13 (6.8)	4 (6.5)	1.00 ^b
COPD, n (%)	13 (5.1)	11 (5.7)	2 (3.2)	0.74 ^b
Sleep apnea, n (%)	7 (2.8)	6 (3.1)	1 (1.6)	1.00 ^b

*Bold values are significant.

^aValue of p for comparison calculated by Student t test.^bValue of p for comparison calculated by Fisher's exact test.

AERD = aspirin-exacerbated respiratory disease; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; SD = standard deviation.

by otolaryngologists, and then other providers. In patients with diagnostic delay, there was a significant difference in provider specialty at time of symptom onset, with more patients with diagnostic delay being seen by primary care. This may be related to the inherent diagnostic dilemmas and difficulties associated with AERD.

AERD often goes unrecognized and presents a diagnostic dilemma due to disease-specific and healthcare system-specific factors. Both the time course of AERD and the difficulty in linking aspirin to symptoms can lead to underdiagnosis. Recent work by the European Academy of

Allergy and Clinical Immunology highlights the diagnostic dilemma associated with AERD and provides guidelines for aspirin challenge, a diagnostic algorithm, and points out major gaps in knowledge on AERD and unmet needs in treatment.²⁸ Identifying this disease is critical because asthma exacerbations secondary to aspirin sensitivity have significant morbidity and can be costly. Patients with AERD have greater morbidity characterized by more severe asthma, more emergency department visits, more intubations, and more corticosteroid bursts when compared with patients with aspirin-tolerant asthma.¹⁶ In a review of 208

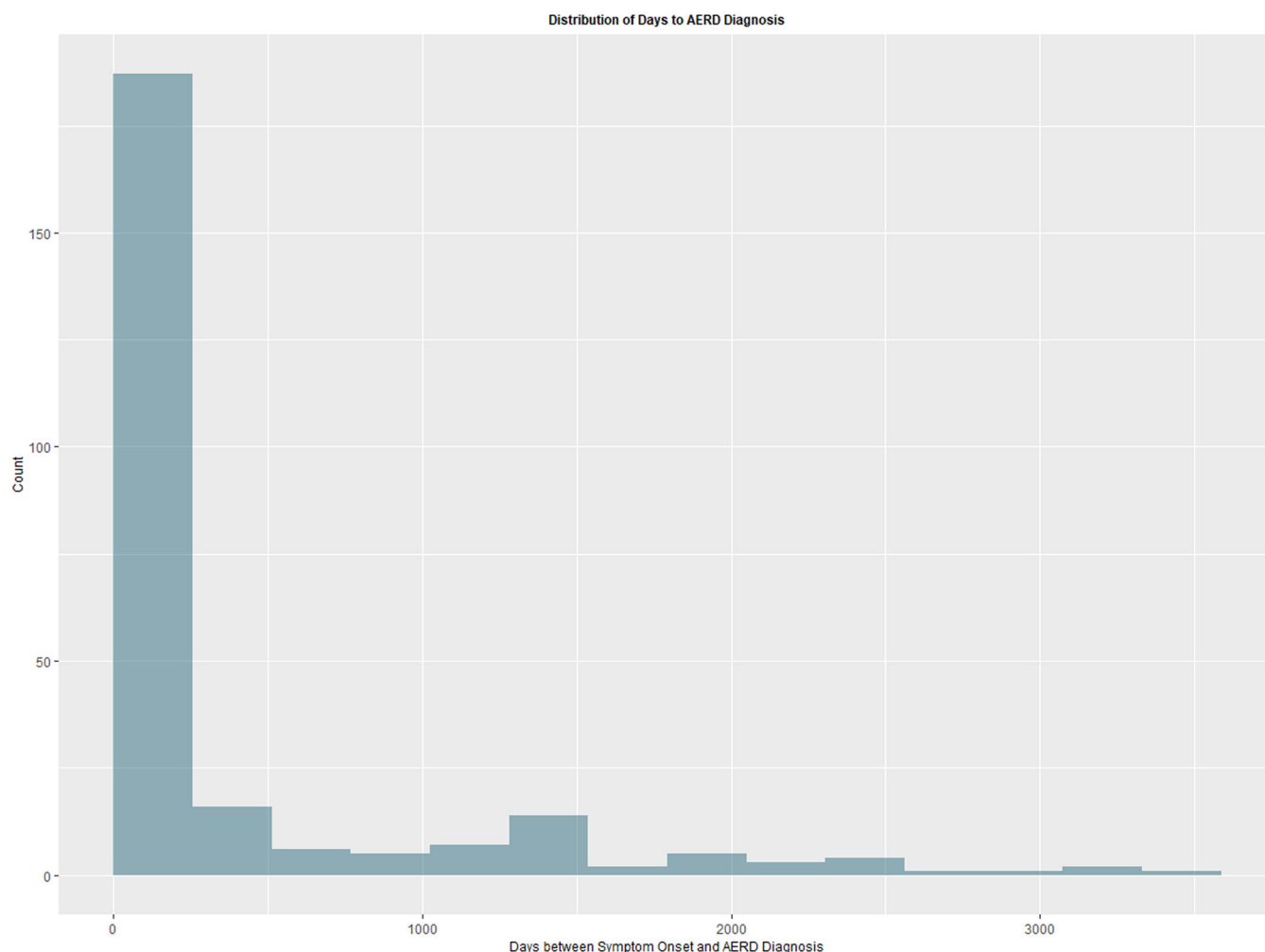


FIGURE 2. Distribution of days to incident AERD diagnosis (number of days between symptom onset and AERD diagnosis). AERD = aspirin-exacerbated respiratory disease.

TABLE 3. Clinical outcomes for AERD patients by differences in delay in diagnosis status *

Clinical outcome	Total (n = 254)	Delay in diagnosis		χ^2 p
		No (n = 192)	Yes (n = 62)	
CT Sinus Lund-Mackay score >6 at index date, n (%) ^a	90 (90.0)	58 (87.9)	32 (94.1)	0.49 ^b
Lower FEV1/FVC of at least 20% compared to baseline, n (%) ^c	7 (7.4)	7 (9.1)	0 (0.0)	0.34 ^b
1+ Sinus surgeries, n (%)	41 (16.1)	31 (16.2)	10 (16.1)	0.99
2+ Courses of systemic steroids, n (%)	91 (35.8)	62 (32.3)	29 (46.8)	0.04
2+ Courses of systemic antibiotics, n (%)	86 (33.9)	61 (31.8)	25 (40.3)	0.22
2+ D-R ER visits, n (%)	25 (9.8)	16 (8.3)	9 (14.5)	0.16
3+ D-R DOV, n (%)	226 (88.9)	175 (91.1)	51 (82.3)	0.05
1+ D-R HA, n (%)	14 (5.5)	9 (4.7)	5 (8.1)	0.34 ^b

*Bold values are significant.

^aFrequency of missing CT Sinus Lund-Mackay score at index date = 154.

^bValue of p for comparison calculated by Fisher's exact test.

^cFrequency of missing FEV1/FVC at either symptom onset or index date = 159.

AERD = aspirin-exacerbated respiratory disease; CT = computed tomography; DOV = doctor's office visits; D-R = disease-related; ER = emergency room; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; HA = hospital admission.

TABLE 4. Provider specialty at symptom onset and AERD diagnosis by delayed diagnosis status*

Parameter	Total (n = 254)	Delay in diagnosis		χ^2 p
		No (n = 192)	Yes (n = 62)	
Provider specialty at symptom onset, n (%)				<0.01
Allergy	83 (32.7)	78 (40.6)	5 (8.1)	
Otolaryngology	74 (29.1)	62 (32.3)	12 (19.4)	
Primary care/pulmonology/other	97 (38.2)	52 (27.1)	45 (72.6)	
Provider specialty at AERD diagnosis, n (%)				0.22
Allergy	141 (55.5)	101 (52.6)	40 (64.5)	
Otolaryngology	92 (36.2)	73 (38.0)	19 (30.7)	
Primary care	21 (8.3)	18 (9.4)	3 (4.8)	

*Bold values are significant.

AERD = aspirin-exacerbated respiratory disease.

patients undergoing functional endoscopic sinus surgery (FESS), patients with AERD underwent approximately 10 times as many FESS procedures.⁷ Also, patients with aspirin sensitivity have higher 22-item Sino-Nasal Outcome Test (SNOT-22) scores and quicker relapse after surgery.²⁹

Diagnostic dilemmas have been identified in various areas of otolaryngology. In oral cavity cancer²¹ and oropharyngeal squamous cell carcinoma,^{19,20} diagnostic delays lead to poor outcomes and decreased survival. The dilemma is evident in chronic sinusitis, in which the symptoms overlap with other common conditions, including allergic rhinitis and viral upper respiratory tract infection.³⁰ Thus, a clinical diagnosis of sinusitis can be inaccurate. A retrospective review of 114 patients with newly diagnosed chronic sinusitis in emergency or primary care settings found only 1 patient met diagnostic criteria.³¹ Another study showed that only 29% and 1% of CRS diagnoses by otolaryngologists and primary care physicians, respectively, met diagnostic criteria.³² A diagnostic dilemma also exists in

allergic fungal sinusitis.³³ Further studies should establish what is considered an acceptable delay in diagnosis for AERD. It will be difficult to determine this standard until clinical outcome measures are well defined.

Diagnostic delay and clinical outcomes

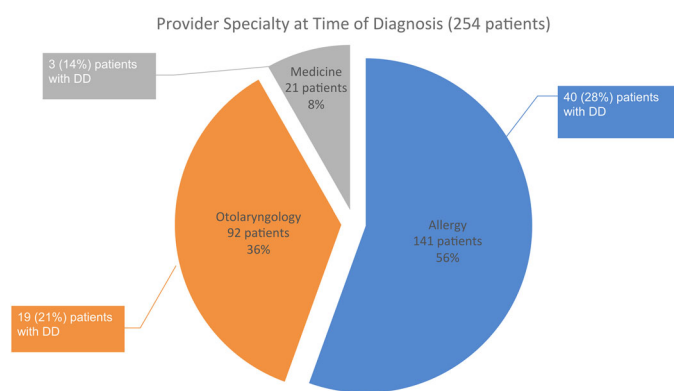
Clinical outcomes and instruments to study them have been well-established in the treatment of CRS.³⁴ Nonetheless, there are still no CRS quality metrics that assess patient outcomes after treatment, such as a minimum degree of change in symptoms, quality of life, or work productivity.³⁵ In the asthma literature, clinical outcomes have been standardized for exacerbations,³⁶ quality of life,³⁷ and other factors.³⁸ No standardized outcomes have been defined for the treatment of patients with AERD. Further areas of study should define clinical outcomes and benchmarks for improvement in the treatment of patients with AERD.

We found a statistically significant association between diagnostic delay and receiving 2 or more courses of systemic steroids, but no significant associations between diagnostic delay and other poorer clinical outcomes. However, it is still plausible that a delay in diagnosis would lead to poorer clinical outcomes.

Limitations

There is no benchmark for what is an acceptable diagnostic delay in chronic disease. For a rare condition such as AERD, which has significant quality of life implications for patients, we have shown that there is often a delay in diagnosis, but the implications of delay are still unclear. We used 1 year as a benchmark timeframe for diagnostic delay based on our clinical experience. Other diagnostic delay timeframes may be considered, and further sensitivity analysis can help to determine an appropriate duration.

Another limitation of our study, aside from the inherent limitations of a retrospective data-only study, is the variability of diagnosis codes for each of the subconditions that constitute AERD. There are potentially patients with asthma, CRSwNP, and ASA or NSAID sensitivity but with no diagnosis of “AERD,” “Aspirin Sensitivity,” or “Hx of Aspirin Sensitive Asthma w Nasal Polyp.” These patients would be unintentionally excluded from our cohort analysis. The study code search was expanded to include addition of “Aspirin Sensitivity” and “Hx of Aspirin Sensitive Asthma” to capture additional potential AERD patients. In addition to using the bundled code for AERD, charts of patients who met combinations of separate criteria (for chronic sinusitis, asthma, and aspirin sensitivity) were reviewed to determine if the diagnosis was made. Cahill et al.²³ showed that chart review based on diagnosis codes and clinical parameters can demonstrate an 88.7% positive predictive value for identifying AERD. Nonetheless, the focus of this study was not on inaccurate diagnosis, but rather on patients who have been diagnosed with AERD in our healthcare system and evaluating whether diagnostic delay affects their clinical outcomes. Additionally, clinical

**FIGURE 3.** Provider specialty at time of diagnosis. DD = delay in diagnosis.

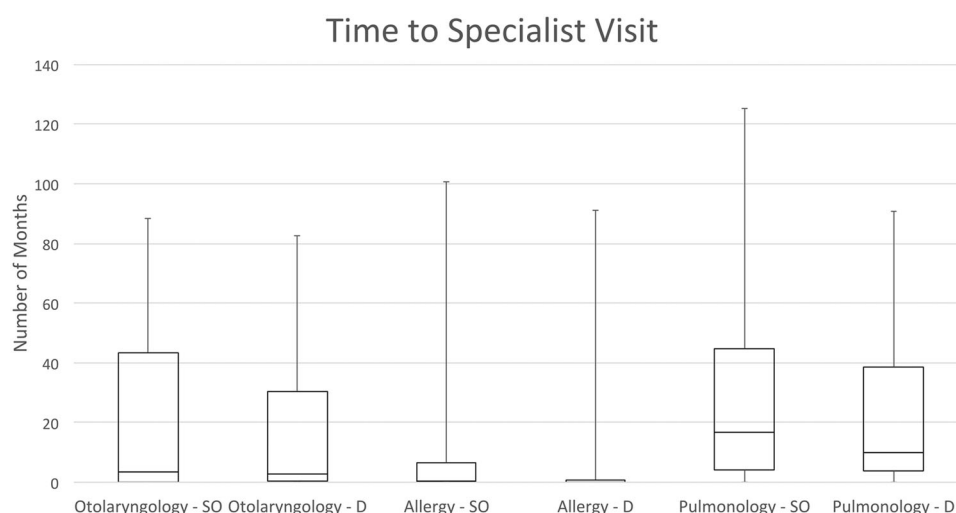


FIGURE 4. Time to specialist visit. Side-by-side box and whisker plot displaying time to specialist visit. D = diagnosis; SO = symptom onset.

TABLE 5. Comparison of other large AERD cohort studies

Study/location	Patients, n	Age at onset (years) (mean $\pm$ SD)	Female %	Race/ethnicity	Findings
Szczeklik et al. ¹⁵ (2000)/Europe	500	45.2 $\pm$ 12.5	70	N/A	Atopy, present in approximately one-third of patients, led to earlier manifestation of rhinitis and asthma, but not of aspirin intolerance or nasal polyposis.
Berges-Gimeno et al. ¹⁴ (2002)/United States	300	34 $\pm$ 12.0	57	Predominantly European; 75% of patients with heterogeneous ethnic background	The disease progressed between historical onset and current evaluation, with more sinusitis and need for controller medications over time. There was no ethnic or familial distribution of AERD.
Mascia et al. ¹⁶ (2005)/United States	459	49.9 $\pm$ 14.3	78	75% white; 15% black; 1% Asian; 7% Hispanic	AERD patients were more likely to have severe asthma, to have been intubated, to have a steroid burst in the previous 3 months, and to have required high-dose inhaled corticosteroids.
Kshirsagar et al. (this study)	254	48.7 $\pm$ 13.4	58.3	59.1% white; 9.8% black; 14.2% Asian; 11.8% Hispanic; 5.1% other	First study in the literature to investigate diagnostic delay for AERD

AERD = aspirin-exacerbated respiratory disease; NA = not available; SD = standard deviation.

outcome data was limited for some subjects who had missing information, including lack of pretreatment or posttreatment CT scans and lack of spirometry data. Finally, not all patients in the study were diagnosed via aspirin challenge.

Conclusion

This is the first study to investigate diagnostic delay in the AERD population and evaluate the diagnostic intricacies

and challenges of a complex chronic disease managed by multiple specialties. Approximately one-quarter of patients with AERD experienced diagnostic delay. Patients with allergies had a lower risk of diagnostic delay. In our study cohort, most patients were diagnosed by an allergist or an otolaryngologist. Future avenues for study include prospective studies with larger sample sizes confirming the clinical course of AERD. In addition, there is an important need for defining clinical outcomes and benchmarks in the care of AERD patients. 🌐

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