

## Original Article

# A Structured Approach to Specialist-referred Difficult Asthma Patients Improves Control of Comorbidities and Enhances Asthma Outcomes

Tunn Ren Tay, MRCP<sup>a,\*</sup>, Joy Lee, FRACP<sup>a</sup>, Naghmeh Radhakrishna, FRACP<sup>a</sup>, Fiona Hore-Lacy, BSc<sup>a</sup>, Robert Stirling, FRACP<sup>a,b</sup>, Ryan Hoy, FRACP<sup>a,c</sup>, Eli Dabscheck, FRACP<sup>a,b</sup>, Robyn O'Hehir, PhD<sup>a,b</sup>, and Mark Hew, PhD<sup>a,c</sup> Melbourne, Victoria, Australia

**What is already known about this topic?** Difficult asthma is highly heterogeneous and a systematic approach to management is recommended by guidelines. However, outcomes of such an evaluation and management in difficult asthma are scarce.

**What does this article add to our knowledge?** A structured approach to difficult asthma management improves asthma symptoms and asthma exacerbations. Improved control of important asthma-related comorbidities likely contributed to the observed improvement in outcomes.

**How does this study impact current management guidelines?** This article provides a detailed description of our structured approach, which can be replicated in other institutions.

**BACKGROUND:** Systematic evaluation is advocated for difficult asthma, but how best to deliver such care is unclear and outcome data are scarce.

**OBJECTIVE:** We describe our institution's structured approach to difficult asthma management and report on the outcomes of such an approach.

**METHODS:** Eighty-two consecutive patients with difficult asthma referred to our clinic from respiratory specialists were evaluated in 3 key areas: diagnostic confirmation, comorbidity detection, and inflammatory phenotyping. We then optimized treatment including relevant comorbidity interventions. The outpatient protocol was supported by comorbidity questionnaires, an electronic clinic template, and standardized panel discussion. Asthma outcomes were assessed at 6 months. **RESULTS:** Sixty-eight patients completed follow-up. Asthma diagnosis was refuted in 3 patients and the remaining 65 patients were included in the study analysis. There was no overall

escalation of inhaled or oral corticosteroids. Patients had a median of 3 comorbidities, and a median of 3 comorbidity interventions. Control of chronic rhinosinusitis and dysfunctional breathing improved among patients with these diagnoses (22-item Sino-Nasal Outcome Test score from  $47 \pm 20$  to  $37 \pm 22$ ,  $P = .017$ ; Nijmegen score from  $32 \pm 6$  to  $25 \pm 9$ ,  $P = .003$ ). There were overall improvements in the Asthma Control Test score (from  $14 \pm 5$  to  $16 \pm 6$ ,  $P < .001$ ), the Asthma Quality of Life Questionnaire (from  $4.29 \pm 1.4$  to  $4.65 \pm 1.5$ ,  $P = .073$ ), and the frequency of exacerbations over 6 months (from 2 [interquartile range, 0-4] to 0 [interquartile range, 0-2],  $P < .001$ ).

**CONCLUSIONS:** In patients referred with difficult asthma from respiratory specialists, a structured approach coupled with targeted comorbidity interventions improved control of key comorbidities and enhanced asthma outcomes. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

**Key words:** Asthma; Systematic assessment; Difficult; Severe; Comorbidity

<sup>a</sup>Allergy, Asthma and Clinical Immunology Service, The Alfred Hospital, Melbourne, Victoria, Australia

<sup>b</sup>Department of Medicine, Monash University, Melbourne, Victoria, Australia

<sup>c</sup>School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

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Corresponding author: Tunn Ren Tay, MRCP, Allergy, Asthma and Clinical Immunology Service, The Alfred Hospital, 55 Commercial Rd, Melbourne, Victoria 3004, Australia. E-mail: [tunn\\_ren\\_tay@cgh.com.sg](mailto:tunn_ren_tay@cgh.com.sg).

\*Tunn Ren Tay is currently at the Department of Respiratory and Critical Care Medicine, Changi General Hospital, Singapore. 2213-2198

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Patients with severe asthma are the focus of intense research due to their relative corticosteroid insensitivity.<sup>1,2</sup> The recognition of distinct inflammatory phenotypes within this population<sup>3-6</sup> has driven the development of targeted biological therapies. However, patients with severe asthma are part of a larger and even more heterogeneous group of patients with difficult-to-control asthma (hereafter referred to as difficult asthma). Patients with difficult asthma may have poor asthma control due to severe asthma biology or other factors including comorbidities, poor medication adherence, or persistent environmental triggers.<sup>5,6</sup> Early studies of difficult asthma identified a high prevalence of comorbidities<sup>7,8</sup> that are associated with poor outcomes.<sup>9,10</sup> All these aspects of difficult asthma

*Abbreviations used*

ACT- Asthma Control Test  
 AQLQ- Asthma Quality of Life Questionnaire  
 CRS- chronic rhinosinusitis  
 DB- dysfunctional breathing  
 GINA- Global Initiative for Asthma

should be addressed before consideration of phenotype-specific biological therapies.

Systematic evaluation of difficult asthma was proposed as early as the 1980s<sup>11,12</sup> and the need for such evaluation was emphasized in recent severe asthma guidelines.<sup>13</sup> However, there are limited outcome data for this approach. The UK National Registry for Difficult Asthma Services demonstrated that dedicated severe asthma services improved outcomes in patients with difficult asthma,<sup>14,15</sup> but the 11 participating centers undertook various assessment protocols, so it was not possible to attribute favorable outcomes to a particular algorithm.

In specialist practice at our university hospital, 10% of patients with asthma in clinic were considered to have difficult asthma by their treating specialists, and thought likely to benefit from systematic evaluation.<sup>16</sup> In contrast, the reported prevalence of difficult asthma in a population study conducted in the Netherlands was higher at about 17%, but these patients might not have received specialist review and probably represented a less complex group of patients.<sup>17</sup>

We hypothesized that for this specific group of specialist-referred patients with difficult asthma, systematic evaluation and management based on current guidelines<sup>13</sup> would improve asthma symptom control, asthma-related quality of life, and frequency of asthma exacerbations. We tested our hypothesis in this longitudinal observational study. In addition, we hypothesized that our institution's tailored approach to difficult asthma comorbidity assessment would improve comorbidity outcomes, and postulated the effect of improvement in comorbidity control on observed asthma outcomes.

## METHODS

Our difficult asthma protocol was established in June 2014, and accepts referrals from respiratory specialists throughout the state of Victoria, Australia. Patients were considered to have difficult asthma if the referring specialist had difficulty managing the patient because of 1 or more of the following: diagnostic dilemma, poor symptom control, frequent or severe exacerbations, poor lung function, or the presence of patient factors such as multiple comorbidities or suspected adherence issues complicating management.

Consecutive patients with difficult asthma who underwent systematic evaluation between June 1, 2014, and March 31, 2016, were included in the study. Patients were assessed and managed over 6 months at 3 outpatient visits. Visit 2 took place 2 months after visit 1, whereas visit 3 was scheduled at 6 months after visit 1.

This study was approved by the Alfred Health Ethics Committee (reference no. 285/15) and requirement for informed consent was waived.

## Protocol evaluation

Our protocol focused on 3 key areas emphasized by the European Respiratory Society/American Thoracic Society guidelines<sup>13</sup> on severe asthma (Figure 1). These key areas are (1) confirming the

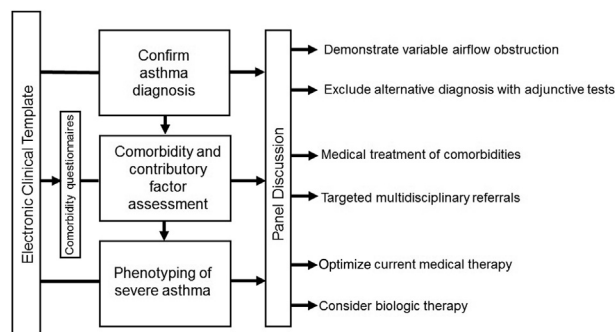


**FIGURE 1.** Systematic evaluation and delivery of a multidimensional assessment at protocol visit 1.

diagnosis of asthma, (2) assessing comorbidities and contributory factors, and (3) establishing the severe asthma phenotype(s).

To achieve a standardized evaluation process, we used 3 support tools that consisted of a questionnaire battery to detect and assess comorbidities, an electronic clinic template using the Research Electronic Data Capture programme,<sup>18</sup> and a panel discussion to ensure protocol adherence. Further details of these tools are provided below.

**Confirming the diagnosis of asthma.** Where possible, we confirmed variable airflow obstruction on the basis of bronchodilator response, peak flow variability, or bronchial provocation testing using mannitol. Protocol physicians were also asked specifically to indicate the clinical probability of asthma. If clinically indicated, adjunctive investigations such as lung volumes and diffusion capacity, chest computed tomography, echocardiography, and cardiopulmonary exercise testing were performed to exclude alternative diagnoses.

**Assessing comorbidities and contributory factors.** All patients were assessed for 8 comorbidities: obesity, allergic rhinitis, chronic rhinosinusitis (CRS), gastroesophageal reflux, obstructive sleep apnea, anxiety or depression, dysfunctional breathing (DB), and vocal cord dysfunction. This was assisted by the administration of validated questionnaires (see Appendix E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).<sup>19-28</sup> We have recently demonstrated the utility of these screening questionnaires in improving the detection of comorbidities in difficult asthma.<sup>29</sup> The diagnostic definition for each comorbidity is described in Table I.

A history of potential aggravating factors such as environmental exposure and poor medication adherence was obtained on the basis of patient report, and structured physician and nursing assessment. All patients underwent asthma nurse education to ensure correct inhaler technique and to reinforce medication adherence. Where indicated, inhaler devices were changed. Toward the end of this series, it became possible to provide a small subset of patients with an electronic dose monitoring device with reminder functions, the Smartinhaler device (Adherium, Auckland, New Zealand), to improve medication adherence. The Smartinhaler device can be affixed on metered dose inhaler, turbuhaler, or accuhaler devices. The Smartinhaler device records the number of as well as the date and time of each dose actuation, and the recorded data can be downloaded for review on the computer. In addition, visual-audio alarms can be set on the Smartinhaler device to serve as medication reminders. The general literacy of our study population was high, as evidenced by the ability of most of our patients to complete the questionnaires adequately. Specialist asthma nurses reviewed all

**TABLE 1.** Diagnosis of extrapulmonary comorbidities

|                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allergic rhinitis                                                                                                                                                                                                                                                   |
| Clinical diagnosis made by allergist                                                                                                                                                                                                                                |
| AND                                                                                                                                                                                                                                                                 |
| Positive skin prick test result OR serum specific IgE to common aeroallergens                                                                                                                                                                                       |
| Chronic rhinosinusitis                                                                                                                                                                                                                                              |
| Presence of compatible clinical symptoms (2 or more of the following symptoms for at least 3 months: nasal congestion, nasal discharge, facial pressure, or decreased sense of smell)                                                                               |
| AND                                                                                                                                                                                                                                                                 |
| Visible sinus opacification on computed tomography OR clinical evidence of sinusitis on ear, nose, and throat (ENT) specialist examination                                                                                                                          |
| Dysfunctional breathing                                                                                                                                                                                                                                             |
| Compatible clinical symptoms (symptoms of dyspnea or chest tightness particularly when associated with a normal peak flow or spirometry reading, lack of improvement with bronchodilators, and improvement after controlled breathing) AND Nijmegen score $\geq 23$ |
| Vocal cord dysfunction                                                                                                                                                                                                                                              |
| Compatible clinical symptoms (presence of throat symptoms especially if associated with other symptoms of laryngeal hypersensitivity with typical sensitivity triggers such as strong odors) AND Pittsburgh vocal cord dysfunction index (PVCDI) $\geq 4$           |
| OR                                                                                                                                                                                                                                                                  |
| Diagnosis of VCD made by ENT specialist                                                                                                                                                                                                                             |
| Obesity                                                                                                                                                                                                                                                             |
| Based on body mass index (BMI) $\geq 30$ kg/m <sup>2</sup>                                                                                                                                                                                                          |
| Obstructive sleep apnea                                                                                                                                                                                                                                             |
| Clinical symptoms (symptoms of snoring, apnea, unrefreshed sleep, or daytime somnolence) AND Berlin questionnaire score $\geq 2$                                                                                                                                    |
| OR                                                                                                                                                                                                                                                                  |
| Previous positive polysomnogram                                                                                                                                                                                                                                     |
| Gastroesophageal reflux disease (GERD)                                                                                                                                                                                                                              |
| Reflux symptoms AND gastroesophageal reflux disease questionnaire (GERDQ) score $\geq 2$                                                                                                                                                                            |
| OR                                                                                                                                                                                                                                                                  |
| Known history of GERD and currently on acid suppression medication                                                                                                                                                                                                  |
| Anxiety and depression                                                                                                                                                                                                                                              |
| Clinical symptoms (patient- or family-reported symptoms of anxiety, stress, or low moods) AND Hospital Anxiety & Depression Score (HADS) score (either anxiety, depression, or both) of $\geq 11$                                                                   |
| OR                                                                                                                                                                                                                                                                  |
| Known history of anxiety/depression and currently on anxiolytics/antidepressants                                                                                                                                                                                    |

patients in clinic and provided asthma education and reinforced asthma action plans. Asthma education and action plans were taught to patients' care providers when deemed necessary.

**Asthma phenotyping.** Atopic status was determined by skin prick testing or serum specific IgE to common aeroallergens. Eosinophilic asthma was defined by the detection of peripheral blood eosinophils ( $\geq 0.3 \times 10^9/L$ ) or fractional exhaled nitric oxide level of more than 35ppb.

**Electronic clinic template and panel discussion.** We custom-built an electronic clinic template to assist the protocol physician to address each key area outlined by the guidelines. We also

commenced a standardized panel discussion at visit 1 attended by 4 asthma specialists, each with further subspecialty interests relevant to difficult asthma. Patients were not included in the panel discussion. Electronic prompts guided the panel discussion to confirm asthma diagnosis, manage comorbidities, and refine the management plan.

### Protocol intervention

**Diagnostic testing.** If there was an indication of an alternative diagnosis to asthma, clinicians were prompted to request further investigations.

**Asthma management.** The patient's asthma management was directed by Global Initiative for Asthma guidelines.<sup>30</sup> If asthma control remained inadequate, physicians were prompted to consider the stepwise escalation of asthma therapy or recruitment into a clinical trial. The clinical trial that was ongoing during the duration of our study was a randomized, double-blind, placebo-controlled phase 3 study of an anti-IL5 receptor  $\alpha$  antibody.<sup>31</sup>

**Comorbidity management.** For each comorbidity detected, the protocol physician was electronically prompted to consider a structured list of management options. This included pharmacological and nonpharmacological measures, or referral for subspecialist assessment and treatment. Management of identified comorbidities was instituted during the time period from visit 1 to visit 2.

### Protocol outcomes

We compared asthma symptom control and quality of life at baseline and 6 months, using the Asthma Control Test (ACT)<sup>32</sup> and the Asthma Quality of Life Questionnaire (AQLQ),<sup>33</sup> respectively. The ACT score ranges from 5 to 25, with a higher score reflecting better asthma control. A change of 3 or more in score represents a clinically meaningful change.<sup>34</sup> The AQLQ score is the mean of 32 disease-specific quality-of-life questions. A lower score represents greater impairment of health status. A change of 0.5 or more in score represents a clinically meaningful change.<sup>35</sup>

Asthma exacerbations were defined as the need for systemic corticosteroids for 3 or more days. Exacerbations and health care utilization (asthma-related hospitalizations, emergency department visits, and primary care visits) occurring in the 6 months before visits 1 and 3 were assessed.

Treatment outcomes of comorbidities were assessed at visit 3. We previously demonstrated that of the comorbidities evaluated in our protocol, CRS, DB, vocal cord dysfunction, and obesity were independent risk factors for our asthma outcomes of interest.<sup>9</sup> Objective outcome measures of CRS and DB, but not vocal cord dysfunction, were available at the time of study initiation. The 22-item Sino-Nasal Outcome Test and Nijmegen questionnaire were administered at the start and end of the difficult asthma protocol to assess the response to treatment of CRS<sup>36</sup> and DB,<sup>37</sup> respectively. The 22-item Sino-Nasal Outcome Test is a rhinosinusitis-specific symptom and health-related questionnaire, with higher scores reflecting worse symptom control. A change in score of 9 has been found to be clinically meaningful.<sup>38</sup> The Nijmegen questionnaire was developed as a screening questionnaire<sup>28</sup> to diagnose dysfunctional breathing, with scores of 23 or more supporting the diagnosis of DB. A decrease and normalization of scores following successful breathing retraining has been reported.<sup>37</sup>

### Statistical analysis

Data were analyzed using SPSS version 22 (IBM, Armonk, NY). Categorical variables were expressed as number (percentages).

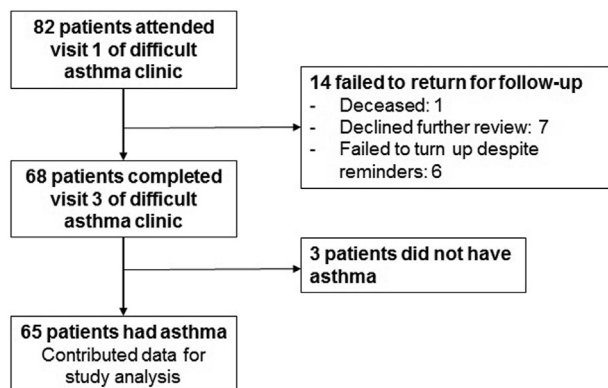


**FIGURE 2.** Flowchart of patients included in study analysis.

Continuous variables were expressed as mean  $\pm$  SD for the variables of age, age of asthma onset, duration of asthma, spirometric measures, ACT, AQLQ, and dose of corticosteroids, and median (interquartile range) for the variables of smoking pack-years, frequency of exacerbations, and frequency of health care utilization. Comparisons of outcome measures between visits 1 and 3 were conducted using McNemar test, the paired  $t$  test, or Wilcoxon matched pair test as appropriate. A  $P$  value of less than .05 was taken to be statistically significant.

## RESULTS

### Protocol evaluation

**Study population.** During the study period, 82 patients were expected to have completed the protocol assessment (Figure 2). Twenty-one patients (25.6%) were referred from respiratory specialists in nonmetropolitan centers in Victoria, and the rest were referred from respiratory specialists in metropolitan centers. Of the 82 patients, 14 patients (17.1%) were lost to follow-up: 1 patient died from presumptive asthma exacerbation, 7 declined further review, and 6 did not return for review despite multiple reminders. The patient who passed away from presumptive asthma was a 52-year-old male with underlying lymphoma, alcohol dependence, and active smoking, who was found collapsed at home. He had been noted to be nonadherent to asthma medications at visit 1. The 14 patients who were lost to follow-up were younger and had better lung function compared with the 68 patients (82.9%) who attended the third clinic visit (see Appendix E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The median (interquartile range) duration of follow-up was 7 (5-11) months.

**Diagnostic assessment.** Following assessment, 3 patients were found not to have a diagnosis of asthma: 2 patients had DB and 1 patient had vocal cord dysfunction. Of the 65 patients with a clinical diagnosis of asthma, 59 demonstrated variable airflow obstruction (43 patients had reversibility demonstrated on spirometry, 8 patients had positive mannitol challenge test results, and 8 patients had peak flow variability). The 6 patients without demonstrable variable airflow obstruction were diagnosed with asthma on the basis of a compatible clinical history and exclusion of alternative diagnoses. All but 2 of the 65 patients with asthma were able to tolerate high-dose inhaled corticosteroid/long-acting beta agonist therapy due to

**TABLE II.** Baseline characteristics of patients with confirmed asthma

| Completed protocol assessment (n = 65)                                                                          |                   |
|-----------------------------------------------------------------------------------------------------------------|-------------------|
| Demographic characteristics                                                                                     |                   |
| Age (y), mean $\pm$ SD                                                                                          | 54 $\pm$ 14       |
| Sex: female, n (%)                                                                                              | 41 (63.1)         |
| White race, n (%)                                                                                               | 61 (93.8)         |
| Smoking status, n (%)                                                                                           |                   |
| Never                                                                                                           | 36 (55.4)         |
| Ex-smoker                                                                                                       | 26 (40)           |
| Current                                                                                                         | 3 (4.6)           |
| Asthma history                                                                                                  |                   |
| Age of asthma onset (y), mean $\pm$ SD                                                                          | 24 $\pm$ 20       |
| Early onset asthma (<18 y), n (%)                                                                               | 33 (48.5)         |
| Duration of asthma (y), mean $\pm$ SD                                                                           | 31 $\pm$ 19       |
| Previous ICU admission, n (%)                                                                                   | 2 (3.1)           |
| Prebronchodilator FEV <sub>1</sub> %, mean $\pm$ SD                                                             | 65 $\pm$ 20       |
| FEV <sub>1</sub> /FVC, mean $\pm$ SD                                                                            | 63 $\pm$ 14       |
| Blood eosinophil ( $10^9$ cells/L), mean $\pm$ SD                                                               | 0.321 $\pm$ 0.319 |
| FENO (ppb*), mean $\pm$ SD                                                                                      | 40 $\pm$ 33       |
| FENO >35 ppb, n (%)                                                                                             | 20 (30.8)         |
| Absolute peripheral blood eosinophils ( $\geq 0.3 \times 10^9$ /L), n (%)                                       | 28 (43.1)         |
| Eosinophilia based on absolute peripheral blood eosinophils ( $\geq 0.3 \times 10^9$ /L) or FENO >35 ppb, n (%) | 36 (55.4)         |
| Atopic, n (%)                                                                                                   | 42 (64.6)         |
| ACT, mean $\pm$ SD                                                                                              | 14 $\pm$ 5        |
| AQLQ, mean $\pm$ SD                                                                                             | 4.33 $\pm$ 1.4    |
| Exacerbation history                                                                                            |                   |
| Asthma exacerbations over past 6 mo, median (IQR)                                                               | 2 (0-4)           |
| Asthma-related hospital admissions over past 6 mo, median (IQR)                                                 | 0 (0)             |
| Asthma-related ED visits over past 6 mo, median (IQR)                                                           | 0 (0-1)           |
| Asthma-related primary care visits over past 6 mo, median (IQR)                                                 | 1 (0-3)           |

ED, Emergency department; FENO, fractional exhaled nitric oxide; FVC, forced expiratory volume; ICU, intensive care unit; IQR, interquartile range.

\*FENO performed in only 52 patients.

unacceptable throat symptoms despite trial of different devices. Subsequent data analysis presented in this study is based only on the 65 patients with a clinical diagnosis of asthma. The baseline characteristics of the 65 patients are presented in Table II.

**Phenotype assessment.** Most patients (86.2%) with a clinical diagnosis of asthma were either eosinophilic or atopic. Twenty (30.8%) were eosinophilic on the basis of peripheral blood eosinophil ( $\geq 0.3 \times 10^9$ /L) or fractional exhaled nitric oxide ( $>35$ ppb), 14 (21.5%) were atopic on the basis of positive skin prick testing or the presence of serum specific IgE to common aeroallergens, and 22 (33.8%) were both eosinophilic and atopic.

**Comorbidity and contributory factor assessment.** The prevalence of comorbidities in patients with a clinical diagnosis of asthma is depicted in Figure 3. A median of 3 (1-4) comorbidities were identified in each patient. Each of the following was present in 30% or more patients: obesity, CRS, DB, vocal cord

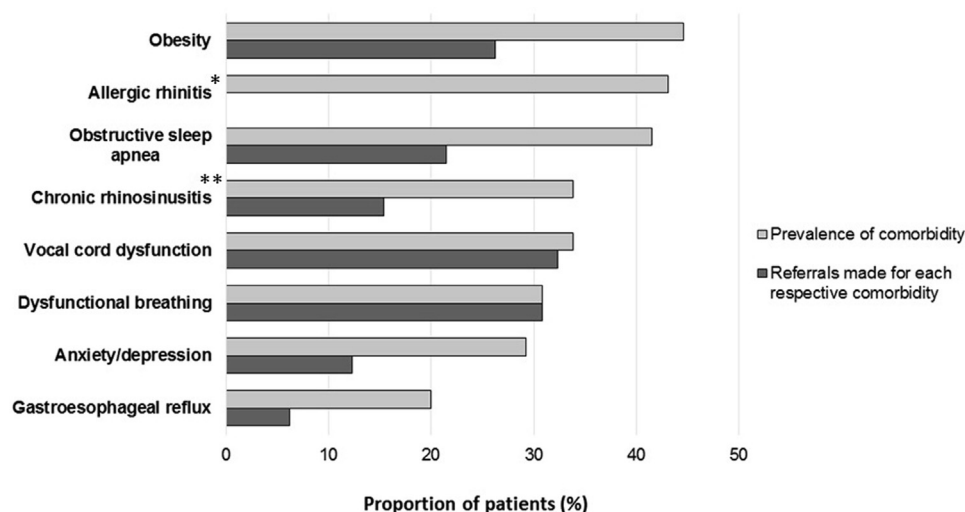


**FIGURE 3.** Prevalence of comorbidities and referrals made for each respective comorbidity. Referrals for the respective comorbidities: obesity, dietician and/or metabolic clinic; obstructive sleep apnea, sleep clinic; CRS, ear, nose and throat (ENT) specialists; vocal cord dysfunction, voice clinic; DB, physiotherapist; anxiety or depression, psychologists; gastroesophageal reflux, gastroenterologists. \*No referrals were made for allergic rhinitis because it was managed by allergists within the difficult asthma service, who delivered medical treatment for CRS as well. \*\*Only patients thought to require sinus surgery were referred to ENT.

**TABLE III.** Comparison of medications at visit 1 and visit 3 in patients with confirmed asthma

| n = 65                                                       | Visit 1   | Visit 3   | P value |
|--------------------------------------------------------------|-----------|-----------|---------|
| ICS dose (fluticasone propionate equivalent) (μg), mean ± SD | 897 ± 438 | 999 ± 449 | .053    |
| OCS dose (mg), mean ± SD                                     | 10 ± 8    | 9 ± 5     | .36     |
| Number on OCS, n (%)                                         | 13 (20)   | 16 (24.6) | .543    |
| Omalizumab, n (%)                                            | 0         | 2 (3.1)   | .5      |
| Anti-IL-5 receptor mAb trial, n (%)                          | 1 (1.5)   | 5 (7.7)   | .125    |
| LTRA, n (%)                                                  | 12 (18.5) | 11 (16.9) | 1       |
| LAMA, n (%)                                                  | 13 (20)   | 17 (26.2) | .344    |
| Theophylline, n (%)                                          | 4 (6.2)   | 2 (3.1)   | .5      |

ICS, Inhaled corticosteroid; OCS, oral corticosteroid; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

dysfunction, allergic rhinitis, and probable sleep apnea. In addition, a history of nasal polyps was reported by 17 patients (26.2%) and aspirin sensitivity was reported by 5 patients (7.7%). Neither nasal polyposis nor aspirin sensitivity was considered as independent comorbidities *per se*.

Smart inhalers were available for use in our difficult asthma clinic only from May 2015. Therefore, of the 65 patients with asthma, objective monitoring of medication adherence using Smart inhalers was possible in only 15 patients. Patients who received Smart inhalers were aware of the dose monitoring function of the devices. Median medication adherence rate of these 15 patients was 87% (79%-95%).

### Protocol intervention

**Diagnostic testing.** To assist in establishing the diagnosis, 13 patients with an eventual clinical diagnosis of asthma (20%) had further investigations including computed tomography chest, echocardiogram, and cardiopulmonary exercise testing.

**Comorbidity interventions.** The median number of comorbidity interventions in patients with a clinical diagnosis of asthma was 3 (1-3). Pharmacological treatment of sinonasal disease and gastroesophageal reflux disease was initiated or escalated in 29 patients (44.6%) and 5 patients (7.7%), respectively. The total number of subspecialty and allied health referrals for management of identified comorbidities was 94, with a median of 1 (0-2) referrals. Details are shown in Figure 3.

**Asthma medication changes.** A comparison between asthma medications at visit 1 and visit 3 is presented in Table III. Compared with visit 1, patients at visit 3 had slightly higher doses of inhaled corticosteroids, although this was not statistically significant. Oral corticosteroids were initiated in 7 patients, ceased in 4, and continued in 9. The mean dose of oral corticosteroids used did not differ between the 2 visits. More patients were treated with omalizumab or recruited into a clinical trial of a biological agent (anti-IL-5 receptor mAb) by visit 3 compared with visit 1.

**Panel discussion.** Seventeen patients with asthma had their first clinic visit before the adoption of the panel discussion, which commenced 3 months after the inception of our difficult asthma protocol. Of the subsequent 48 patients, 44 (91.7%) underwent panel discussion. Additional treatments were suggested in 19 patients (43.2%), and these recommendations were implemented by the treating clinician in 6 patients. Further subspecialty referrals were suggested in 6 of the 44 patients (13.6%) and these suggestions were carried out in 2 patients.

### Protocol outcomes

**Asthma outcomes.** There was a statistically significant improvement in ACT score from  $14 \pm 5$  to  $16 \pm 6$  ( $P < .001$ ). The AQLQ score improved from  $4.29 \pm 1.4$  to  $4.65 \pm 1.5$ , although this failed to reach statistical significance ( $P = .073$ ) (Figure 4).

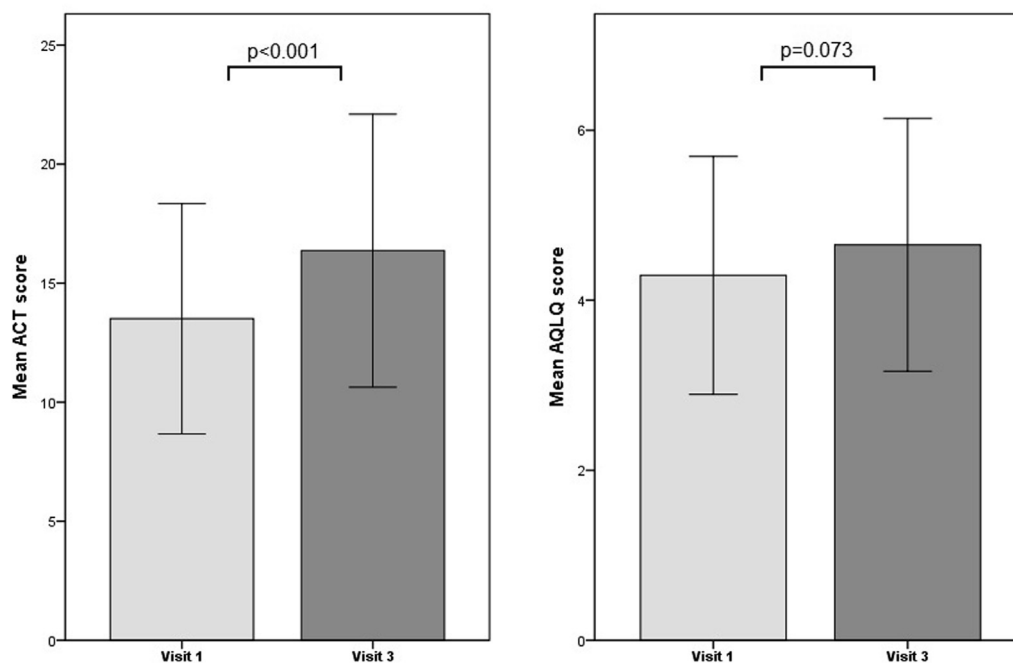


FIGURE 4. Comparison of ACT and AQLQ scores at visit 1 and visit 3. Error bars indicate 1 SD.

TABLE IV. Comparison of asthma outcomes at visit 1 and visit 3 in patients with confirmed asthma

| n = 65                                                     | Visit 1    | Visit 3    | P value |
|------------------------------------------------------------|------------|------------|---------|
| Asthma exacerbations past 6 mo, median (IQR)               | 2 (0-4)    | 0 (0-2)    | <.001   |
| Asthma-related hospital admissions past 6 mo, median (IQR) | 0 (0)      | 0 (0)      | .311    |
| Asthma-related ED visit past 6 mo, median (IQR)            | 0 (0-1)    | 0 (0)      | .142    |
| Asthma-related primary care visits past 6 mo, median (IQR) | 1 (0-3)    | 0 (0)      | <.001   |
| Exacerbations $\geq 1$ , n (%)                             | 47 (72.3%) | 27 (41.5%) | .001    |

ED, Emergency department; IQR, interquartile range.

There was a significant reduction in the median number of asthma exacerbations (from 2 to 0) and the median number of asthma-related primary care visits (from 1 to 0) (Table IV).

Repeat spirometry at visit 3 was limited by laboratory availability; therefore, only 43 patients (66.2%) had a repeat spirometry (median duration of time between visit 3 and repeat spirometry was 0 [0-2] months). In these 43 patients, there was no significant difference in prebronchodilator FEV<sub>1</sub>% at visit 3 (70%  $\pm$  20%) compared with visit 1 (67%  $\pm$  21%) ( $P$  = .146). The prebronchodilator FEV<sub>1</sub>% at visit 1 was not significantly different between those who did or did not have repeat spirometry at visit 3 (67%  $\pm$  21% vs 63%  $\pm$  21%;  $P$  = .515).

**Comorbidity outcomes.** Between visit 1 and visit 3, patients with CRS ( $n$  = 23) had a statistically and clinically significant improvement in the 22-item Sino-Nasal Outcome Test score from 47  $\pm$  20 to 37  $\pm$  22 ( $P$  = .017). Patients with DB ( $n$  = 21) had near normalization of Nijmegen questionnaire scores (normal value <23) from 32  $\pm$  6 to 25  $\pm$  9 ( $P$  = .003).

There was no significant change in body mass index in patients with obesity between visit 1 and visit 3 (37  $\pm$  7 vs 37  $\pm$  6;  $P$  = .636; Figure 5). Of the 3 patients who were active smokers at visit 1, 2 patients continued to smoke at visit 3 despite smoking cessation counseling.

## DISCUSSION

Our study demonstrates 3 key findings regarding patients diagnosed by respiratory specialists to have difficult asthma. First, a systematic approach was associated with improvements in multiple asthma outcomes. Second, control of key comorbidities was enhanced, which probably contributed to the improved asthma outcomes. Third, results were achieved using a structured outpatient approach, which efficiently tailored comorbidity interventions to each patient.

The improvements in ACT score and exacerbation rates were statistically and clinically significant. Our results confirm the benefit of clinical evaluation through dedicated difficult asthma services reported by Gibeon et al.<sup>14</sup> In that cohort, patients underwent various protocols. In contrast, our patients underwent a single defined protocol that we have detailed and that can be replicated elsewhere. The previous study was restricted to severe asthma, whereas we analyzed all patients referred with difficult asthma.

Although our protocol resulted in overall improvement in asthma symptom control and exacerbation rates, 1 patient who was seen in our difficult asthma clinic at visit 1 subsequently died from a presumptive asthma exacerbation. The patient was an active smoker and was nonadherent to asthma medications. Smoking cessation counseling and medication adherence were reinforced at the first clinic visit. Unfortunately, the patient failed to attend his subsequent scheduled clinic reviews and passed away 6 months after the first difficult asthma clinic visit. We believe smoking and nonadherence to be the major contributory

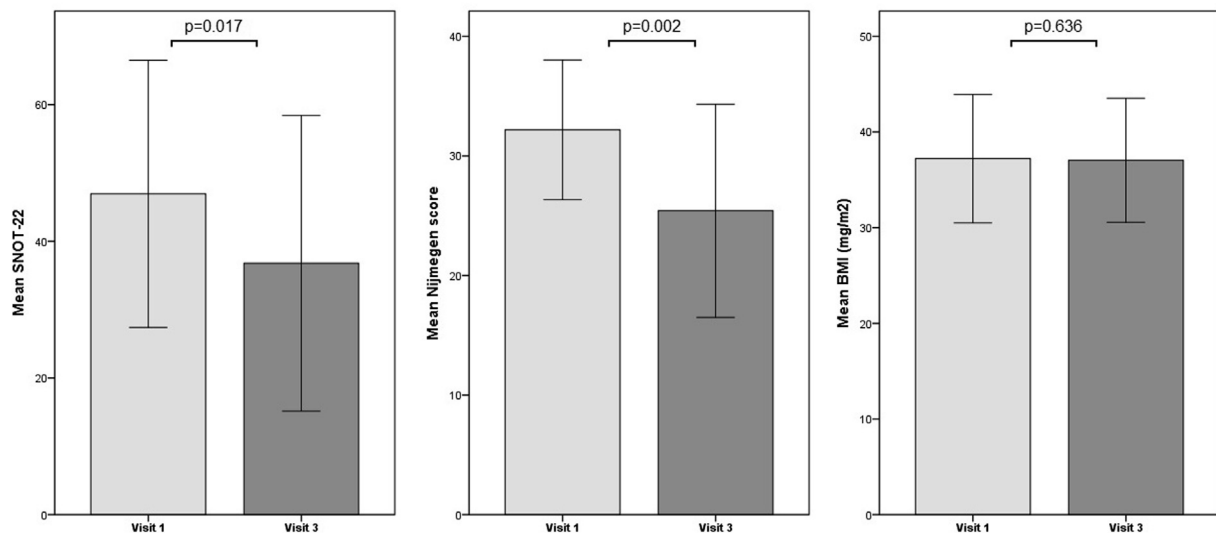


**FIGURE 5.** Changes in SNOT-22, Nijmegen scores, and BMI between visit 1 and visit 3. Error bars indicate 1 SD. *BMI*, Body mass index; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

factors to his poor asthma control and fatal asthma exacerbation. Unfortunately, patients who fail to return for follow-up are likely to have limited benefit from a protocol requiring multiple visits. This study was not powered to detect an effect of our assessment protocol on the risk of asthma death, but the fatality is a reminder that this patient group is at increased risk of mortality.

The improvement in asthma outcomes was not associated with an increase in inhaled corticosteroids or a change in overall maintenance oral corticosteroids. These results are similar to those of previous studies.<sup>15</sup> We did not place any patients on corticosteroid-sparing immunosuppressants. Out of 65 patients with asthma, only 2 patients were commenced on omalizumab in contrast to previous series where up to 13% of patients were placed on omalizumab treatment for severe atopic asthma.<sup>14</sup> Following systematic assessment, 4 additional patients received a trial of biological treatment (or placebo) targeting the IL-5 receptor.

The low rate of omalizumab prescription in our cohort was probably due to the Australian government's requirement for patients to receive 12 months of specialist care before qualifying for subsidized drug. Within the short follow-up of this study, this criterion for prescription was not met by most patients. Furthermore, during the study period, no phenotype-specific biological therapy other than omalizumab was licensed in Australia for treatment of severe asthma. In short, few novel pharmacological interventions were available to this cohort, and the improvements in asthma outcomes were probably not solely due to refinements in drug therapy.

Comorbidities were highly prevalent in our patients, in keeping with findings of other difficult asthma cohorts.<sup>7,8</sup> Most patients had multiple comorbidities. The presence of these comorbidities has been previously associated with asthma.<sup>39-44</sup> We have recently shown on multivariate analysis the independent influence of CRS, obesity, DB, and vocal cord dysfunction on asthma outcomes in this difficult asthma cohort.<sup>9</sup> We therefore analyzed the response to treatment of these 4 specific comorbidities. We observed significant improvements in questionnaire scores used to measure control of CRS and DB.

However, we did not have a validated marker of control for vocal cord dysfunction, and body mass index did not improve despite interventions over at least 6 months, consistent with other studies.<sup>45,46</sup>

How did our structured approach to difficult asthma influence asthma outcomes? Achieving the correct (nonasthma) diagnosis in 3 patients and providing phenotype-specific biologicals in another 2 patients who were initiated on omalizumab probably contributed to their improvement. Asthma education and attempts at checking and improving medication adherence in all patients might also have contributed to improved outcomes, and this aspect of asthma management should be routinely practiced at each consultation. However, we performed multiple interventions for contributory comorbidities in many patients, and the enhanced control of rhinosinusitis and DB suggests that these interventions were generally successful. We therefore postulate that control of key comorbidities may have had the greatest impact on asthma outcomes in our cohort. This explanation may not hold true in other settings, especially those with higher rates of misdiagnosis<sup>47</sup> or more rapid access to biological therapy.<sup>14</sup> Therefore, we believe all aspects of our multidimensional assessment protocol to be necessary for optimal outcomes.

In our protocol, we used a stratified approach to assess and treat comorbidities.<sup>48</sup> The first stratum consisted of comorbidity questionnaires administered at the first outpatient consultation. Such a comprehensive approach was considered necessary because these comorbidities are often underrecognized even by respiratory specialists.<sup>29</sup> Most patients had no difficulty completing the questionnaires, taking an average of 40 minutes to complete them.<sup>29</sup>

The second stratum was the clinical assessment, where the possibility of comorbidities based on questionnaire responses was explored in greater detail. Clinical assessment was therefore supplemented rather than replaced by questionnaire results.

Only patients with a clinical likelihood for a particular comorbidity proceeded to the third stratum of management, that is, specific drug treatment or interdisciplinary referral. This contrasts with the "blanket" approach described in some series,

where every patient might be referred to allergists, ear, nose and throat surgeons, physiotherapists, psychologists, or psychiatrists.<sup>7,8</sup> We believe that our “bespoke” strategy substantially reduced the workload placed on our health service.

Although our study was not designed to examine the health economics impact of asthma-related comorbidities in patients with difficult asthma, we are of the opinion that a tailored approach to evaluate and manage comorbidities is likely to be cost-effective. A large proportion of asthma costs is due to asthma medications and exacerbation-related health care visits.<sup>49,50</sup> Unrecognized or untreated comorbidities results in misdiagnosis of asthma or misattribution of symptoms to asthma. This inevitably leads to unnecessary escalation of treatment, including systemic corticosteroids and novel biologic agents, which adds substantially to treatment costs.<sup>50</sup> There is evidence to suggest that control of certain comorbidities such as obesity,<sup>51</sup> CRS,<sup>52,53</sup> and vocal cord dysfunction<sup>54</sup> can positively impact asthma outcomes. These comorbidity interventions are widely available and affordable in many institutions.

We acknowledge certain limitations in our single-center study. First, 17% of our patients were lost to follow-up, although their baseline characteristics were similar to those who attended follow-up. Second, only two-third of patients had repeat spirometry at the end of the protocol. We acknowledge that spirometry is an important outcome of asthma control, and ideally all patients should have a repeat spirometry. However, spirometric improvement may not be wholly reflective of the efficacy of an asthma intervention.<sup>55</sup> Observational studies from other difficult asthma cohorts similarly did not report a clinically significant improvement in spirometry despite improvement in other important asthma outcomes.<sup>14,56</sup> Third, we were unable to assess medication adherence objectively in the majority of our cohort because the SmartInhaler device was available only a year after the start of our difficult asthma clinic; however, undetected nonadherence would likely have served to dilute the improvement in asthma outcomes. Fourth, we did not demonstrate improved control of every comorbidity, but it may not be necessary to rectify every comorbidity to achieve overall patient benefit. Last, as with other observational studies, we were unable to exclude regression to the mean as a possible explanation for the improvement in asthma outcomes.

In conclusion, a structured approach to specialist-referred patients with difficult asthma improves asthma symptom control and exacerbation frequency. In our particular cohort, targeted multidisciplinary involvement directed toward key comorbidities may have been the greatest contributor to improvement in asthma outcomes. This highlights the central role of systematic evaluation in optimizing *overall* patient care, before treating severe asthma biology with the expensive targeted therapies now entering clinical practice.

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## APPENDIX

## APPENDIX E1. Questionnaires used for screening comorbidities

| Questionnaires            | Comorbidity       | Cutoff value                               | Interpretation                           |
|---------------------------|-------------------|--------------------------------------------|------------------------------------------|
| SNQ <sup>E1,E2</sup>      | Sinonasal disease | $\geq 1$                                   | Chronic sinonasal disease likely present |
| NIJMEGEN <sup>E3,E4</sup> | DB                | $\geq 23$                                  | DB likely present                        |
| PVCDI <sup>E5</sup>       | VCD               | $\geq 4$                                   | VCD likely present                       |
| BERLIN <sup>E6,E7</sup>   | OSA               | $\geq 2$                                   | High risk of sleep apnea                 |
| HADS <sup>E8</sup>        | Anx/Dep           | $\geq 11$ for either anxiety or depression | Anxiety or depression likely present     |
| GERD-Q <sup>E9,E10</sup>  | GERD              | $> 2$                                      | $> 50\%$ chance of GERD                  |

*Anx/dep*, Anxiety or depression; *BERLIN*, BERLIN questionnaire; *GERD-Q*, Gastroesophageal Reflux Disease Questionnaire; *GERD*, gastroesophageal reflux disease; *HADS*, Hospital Anxiety And Depression Scale; *NIJMEGEN*, Nijmegen questionnaire; *OSA*, obstructive sleep apnea; *VCD*, vocal cord dysfunction.

**APPENDIX E2.** Comparison of baseline characteristics of patients who returned for visit 3 and those who did not return for visit 3

| Characteristic                                                                                    | Returned for<br>visit 3 (n = 68) | Did not return<br>for visit 3 (n = 14) | P value |
|---------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------------|---------|
| Demographic characteristics                                                                       |                                  |                                        |         |
| Age (y), mean ± SD                                                                                | 54 ± 14                          | 45 ± 13                                | .031    |
| Sex: female, n (%)                                                                                | 43 (63.2%)                       | 11 (78.6%)                             | .27     |
| White race, n (%)                                                                                 | 64 (94.1%)                       | 13 (92.9%)                             | .341    |
| Smoking status, n (%)                                                                             |                                  |                                        | .196    |
| Never                                                                                             | 37 (54.4%)                       | 9 (64.3%)                              |         |
| Ex-smoker                                                                                         | 28 (41.2%)                       | 3 (21.4%)                              |         |
| Current                                                                                           | 3 (4.4%)                         | 2 (14.3%)                              |         |
| Smoking pack-years, median (IQR)                                                                  | 10 (4-30)                        | 10 (3-43)                              | .758    |
| Asthma history                                                                                    |                                  |                                        |         |
| Age of asthma onset (y), mean ± SD                                                                | 24 ± 21                          | 22 ± 17                                | .715    |
| Early onset asthma (<18 y), n (%)                                                                 | 33 (48.5%)                       | 7 (50%)                                | .92     |
| Duration of asthma (y), mean ± SD                                                                 | 30 ± 19                          | 24 ± 17                                | .291    |
| Prebronchodilator FEV <sub>1</sub> (%), mean ± SD                                                 | 67 ± 21                          | 82 ± 25                                | .017    |
| FEV <sub>1</sub> /FVC, mean ± SD                                                                  | 64 ± 14                          | 70 ± 15                                | .126    |
| Blood eosinophil (10 <sup>9</sup> cells/L), mean ± SD                                             | 0.311 ± 0.315                    | 0.358 ± 0.323                          | .619    |
| FENO (ppb), mean ± SD                                                                             | 40 ± 32                          | 30 ± 21                                | .214    |
| Eosinophilia based on absolute peripheral blood<br>eosinophils (≥0.3 × 10 <sup>9</sup> /L), n (%) | 36 (52.9%)                       | 10 (71.4%)                             | .204    |
| Atopic, n (%)                                                                                     | 43 (63.2%)                       | 9 (64.3%)                              | .315    |
| Medications                                                                                       |                                  |                                        |         |
| ICS dose (fluticasone propionate equivalent) (μg), mean ± SD                                      | 878 ± 459                        | 746 ± 398                              | .322    |
| On oral corticosteroids, n (%)                                                                    | 13 (19.1%)                       | 2 (14.3%)                              | .67     |
| On omalizumab, n (%)                                                                              | 0                                | 0                                      | —       |
| On LAMA, n (%)                                                                                    | 13 (19.1%)                       | 2 (14.3%)                              | .67     |
| On LTRA, n (%)                                                                                    | 12 (17.6%)                       | 4 (28.6%)                              | .348    |
| On theophylline, n (%)                                                                            | 5 (7.4%)                         | 2 (14.3%)                              | .398    |
| Comorbidities                                                                                     |                                  |                                        |         |
| Number comorbidities, median (IQR)                                                                | 3 (1-4)                          | 3 (1-4)                                | .807    |
| Obesity, n (%)                                                                                    | 29 (42.6%)                       | 5 (35.7%)                              | .632    |
| Allergic rhinitis, n (%)                                                                          | 29 (42.6%)                       | 7 (50%)                                | .641    |
| CRS, n (%)                                                                                        | 23 (33.8%)                       | 7 (50%)                                | .252    |
| Gastroesophageal reflux, n (%)                                                                    | 13 (19.1%)                       | 4 (28.6%)                              | .427    |
| Suspected obstructive sleep apnea, n (%)                                                          | 28 (41.2%)                       | 3 (21.4%)                              | .165    |
| Anxiety or depression, n (%)                                                                      | 20 (29.4%)                       | 5 (35.7%)                              | .641    |
| DB, n (%)                                                                                         | 21 (30.9%)                       | 5 (35.7%)                              | .723    |
| Vocal cord dysfunction, n (%)                                                                     | 23 (33.8%)                       | 3 (21.4%)                              | .364    |
| Asthma control                                                                                    |                                  |                                        |         |
| ACT score, mean ± SD                                                                              | 14 ± 5                           | 15 ± 6                                 | .737    |
| AQLQ score, mean ± SD                                                                             | 4.25 ± 1.47                      | 4.5 ± 1.49                             | .624    |
| Asthma exacerbations past 6 mo, median (IQR)                                                      | 2 (0-4)                          | 0                                      | .207    |
| Asthma-related hospital admissions over past 6 mo, median (IQR)                                   | 0 (0)                            | 0                                      | .624    |
| Asthma-related ED visits over past 6 mo, median (IQR)                                             | 0 (0-1)                          | 0                                      | .53     |
| Asthma-related primary care visits over past 6 mo, median (IQR)                                   | 1 (0-3)                          | 0                                      | .336    |

FENO, Fractional exhaled nitric oxide; FVC, forced expiratory volume; ICS, inhaled corticosteroid; IQR, interquartile range; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

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