Original Article

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

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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 ± 20 to 37 ± 22, $P = .017$; Nijmegen score from 32 ± 6 to 25 ± 9, $P = .003$). There were overall improvements in the Asthma Control Test score (from 14 ± 5 to 16 ± 6, $P < .001$), the Asthma Quality of Life Questionnaire (from 4.29 ± 1.4 to 4.65 ± 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*

Patients with severe asthma are the focus of intense research due to their relative corticosteroid insensitivity.[1,2] The recognition of distinct inflammatory phenotypes within this population[3-6] 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.[5,6] Early studies of difficult asthma identified a high prevalence of comorbidities[7,8] that are associated with poor outcomes.[9,10] All these aspects of difficult asthma

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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[11,12] and the need for such evaluation was emphasized in recent severe asthma guidelines.[13] 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,[14,15] 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.[16] 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.[17]

We hypothesized that for this specific group of specialist-referred patients with difficult asthma, systematic evaluation and management based on current guidelines[13] 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[13] on severe asthma (Figure 1). These key areas are (1) confirming the diagnosis of asthma, (2) assessing comorbidities and contributory factors, and (3) establishing the severe asthma phenotype(s).

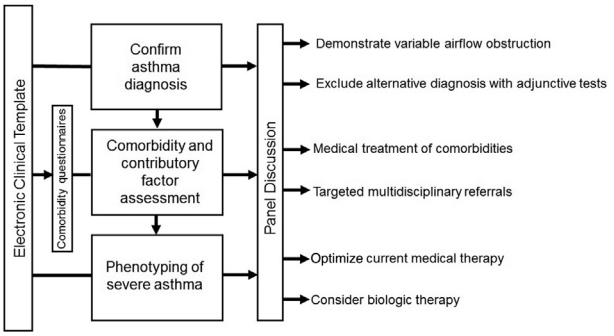

FIGURE 1. Systematic evaluation and delivery of a multidimensional assessment at protocol visit 1.

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,[18] 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).[19-28] We have recently demonstrated the utility of these screening questionnaires in improving the detection of comorbidities in difficult asthma.[29] 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