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Systematic assessment for difficult and severe asthma improves outcomes and halves oral corticosteroid burden independent of monoclonal biologic use.

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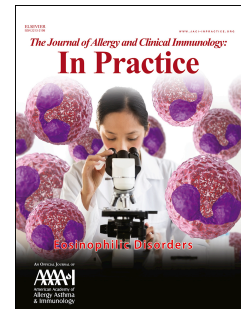
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Systematic assessment for difficult and severe asthma improves outcomes and halves oral corticosteroid burden independent of monoclonal biologic use.

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Abstract*Background*

Guidelines endorse systematic assessment for severe asthma, with data indicating benefit across multiple outcome domains.

Objective

We examined which patients respond to systematic assessment and whether oral corticosteroid burden can be decreased independent of monoclonal biologic use.

Methods

Specialist-referred patients are assessed systematically for difficult asthma at our centre. We undertook a responder analysis for improvements in the domains of symptom control, quality of life, exacerbations and airflow obstruction, assessed six months after initial assessment. Multivariate analyses were performed for each domain to identify predictors of response. Changes in oral corticosteroid burden were also measured, stratified by monoclonal biologics commenced during assessment.

Results

Among 161 patients assessed systematically, 64% had a reduction in exacerbations, 54% achieved minimum clinically important differences for both symptom control and quality of life, and 40% increased their FEV₁ by ≥ 100 ml. Altogether, 87% of asthma patients improved in at least one domain. The most consistent predictor of response across domains was poorer baseline asthma status. There was a substantial reduction in mean chronic oral corticosteroid dose (11 mg to 5 mg, $n=46$, $p<0.001$), even after excluding seven patients commenced on monoclonal biologics (11 mg to 5.6 mg, $n=39$, $p<0.001$).

Conclusion

Almost 90% of patients undergoing systematic assessment for difficult asthma improve significantly in at least one key asthma outcome, with few reliable predictors of response. The halving of oral corticosteroid burden during systematic assessment is independent of, and comparable in magnitude to, that achieved by monoclonal biologics.

Highlights*What is already known about this topic?*

Systematic assessment for severe and difficult asthma is recommended by guidelines with observational studies showing improved outcomes but often at the expense of increased oral corticosteroids. In the era of biologic medications it is unknown whether there remains a role for systematic assessment.

What does this article add to our knowledge?

Almost 90% of patients improve in at least one outcome after protocolised assessment (protocol published and freely available) despite a halving of oral corticosteroid use, independent of monoclonal medications, an improvement similar to that of monoclonal medications themselves.

How does this study impact current management guidelines?

Severe and difficult-to-treat asthma patients who have ongoing symptoms, exacerbations or impaired quality of life should undergo systematic assessment even in the era of biologic medications.

Keywords:

Severe asthma

Difficult asthma

Systematic assessment

Protocolised assessment

Asthma guidelines

Exacerbations

Abbreviations:

FEV1 – Forced expiratory volume in one second

PEF – Peak expiratory flow

AHR – Airway hyperresponsiveness

FeNO – Fractionated exhaled nitric oxide

IgE – Immunoglobulin E

ACQ6 – Asthma control questionnaire 6

AQLQ – Asthma quality of life questionnaire

BMI – Body mass index

Introduction

Approximately five percent of patients with asthma remain poorly controlled, requiring conventional treatment escalation up to and including oral corticosteroids.(1) These patients are at higher risk of exacerbations and mortality as well as corticosteroid adverse effects.

Potential reasons for uncontrolled disease are various and complex, including incorrect diagnosis, uncontrolled comorbidities, poor treatment adherence, and severe asthma biology.(2) Major guidelines therefore recommend multidisciplinary systematic assessment for severe and difficult asthma,(3) with aggregate data from observational studies showing improved asthma outcomes.(4-7)

However, it is unknown how often patients improve after systematic assessment, which patients respond best, and whether these responders are identifiable prior to their assessment. A greater understanding of these issues might help prioritise referrals for assessment and streamline the provision of health services. It is also unclear whether systematic assessment can reduce oral corticosteroid burden, over and above the corticosteroid-sparing effect of monoclonal biologics now available for clinical use. Previous reductions in systemic corticosteroid use following systematic assessment occurred in conjunction with the use of monoclonal biologics.(8)

Among patients undergoing systematic assessment for severe asthma at our centre, we identified and characterised clinical responders across the domains of symptom control, quality of life, exacerbations, and lung function. We further examined whether oral corticosteroid burden was decreased through the assessment period. We also examined how improvements in asthma status and systemic corticosteroid use related to monoclonal biologic use.

Methods

We included consecutive specialist-referred patients assessed systematically for uncontrolled asthma who had initial visits and six-month follow up between 1st June 2014 and 31st December 2017.

Systematic Assessment

The overall aim of the systematic assessment is to identify and manage factors that are resulting in “difficult-to-treat” asthma. These reasons may include poor adherence, poor inhaler technique, uncontrolled comorbidities, misdiagnosis, and/or undertreated severe asthma biology. The treatments that result from systematic assessment are not limited to asthma-specific treatments such as biologics and individuals usually have multiple interventions during the assessment. Our protocol for systematic assessment has been published and is guided by a bespoke electronic template that ensures consistency between physicians.(9, 10) In brief we aim to confirm the asthma diagnosis, assess and improve medication adherence (with electronic monitoring devices where possible), provide asthma and inhaler technique education, complete an asthma self management plan, diagnose and manage comorbidities, and optimise asthma treatment. Asthma education includes information on asthma pathogenesis, treatment, discussion and review of inhaler technique, and self-management strategies and is delivered by a asthma nurse-educator to every patient.

Confirmation of asthma diagnosis was based on demonstration of variable airflow obstruction, defined as $>12\%$ and 200mL improvement in FEV₁ post bronchodilator, or peak flow variability $>20\%$, or positive bronchoprovocation test. There are a minority of patients who have not met these criteria but who are thought by the specialist panel to have underlying asthma despite this (for example those with significant FEV₁ variability between tests). The FEV₁ value reported was obtained prior to bronchodilator, unless otherwise specified.

Asthma control was assessed with the Asthma Control Questionnaire 6 (ACQ6) and quality of life with the Asthma Quality of Life Questionnaire (AQLQ).(11, 12) Exacerbations were defined as an increase in asthma symptoms and/or a worsening of peak flows necessitating ≥ 3 days systemic corticosteroids.(3)

Uncontrolled asthma was considered those with one or more of: ACQ ≥ 1.5 , ≥ 2 severe exacerbations or ≥ 1 serious exacerbation (requiring hospitalization, intensive care admission or mechanical ventilation) and those with FEV₁ $<80\%$ in line with ERS/ATS definitions.(3)

A battery of questionnaires was used to screen for relevant comorbidities which were then confirmed on clinical assessment.(13) Criteria for diagnosis of eight key comorbidities have been published previously and are summarised as follows.(14) Allergic rhinitis: specialist allergist diagnosis in the presence of atopy. Chronic rhinosinusitis: clinical symptoms with a positive CT sinuses or compatible ear, nose and throat (ENT) specialist examination. Chronic rhinosinusitis symptoms were assessed based on the validated Sinonasal Outcome Test (SNOT-22 score).(15) Obstructive sleep apnoea (OSA): symptoms were captured via the Berlin score and diagnosis was based on polysomnography showing Apnoea Hypopnoea

Index >5.(16, 17) Gastro-oesophageal reflux (GORD): compatible clinical symptoms plus an elevated GERD-Q score >2 or known history of GORD on acid suppression medication. Dysfunctional breathing; Nijmegen Questionnaire score > 23 and compatible clinical symptoms or specialist physiotherapist diagnosis.(18, 19) Vocal cord dysfunction (VCD): paroxysmal vocal fold motion on laryngoscopy and/or clinical diagnosis by a specialist in VCD (Ear, Nose and Throat surgeon, speech pathologist or respiratory physician). Symptoms of VCD were assessed by both the Pittsburgh Index and the Vocal Cord Dysfunction-Questionnaire (VCD-Q) scores.(20, 21) Psychiatric history was evaluated in two ways; physician diagnosis (present or absent and actual diagnosis) and elevated Hospital Anxiety and Depression Score (HADS A >11 and D >8).(13)

Socioeconomic status was based on the Socioeconomic Indexes for Areas, a multidimensional postcode-based classification with patients classified by postcode and dichotomised into high (6 or more) versus low (5 or less) socioeconomic status.(22)

Biomarkers were assessed in all patients at baseline and positivity was defined as: Immunoglobulin E (IgE) ≥ 75 (23), blood eosinophils ≥ 300 cells/uL, fractional exhaled nitric oxide (FeNO) ≥ 25 ppb.(24) A panel of blood tests included a vasculitis screen, vitamin D, and serum specific IgE and skin prick testing to a range of common aeroallergens. Atopy was defined as the presence of a positive skin prick test and/or positive serum specific IgE testing to common allergens.

Each case was presented at a panel discussion attended by three respiratory and allergy specialists. Asthma medications were optimised based on panel consensus. All patients underwent asthma education and inhaler technique assessment by an experienced asthma nurse and, where possible, formal electronic monitoring of inhaler adherence.(25, 26)

Relevant allied health and specialist referrals were arranged, with access to speech pathology for vocal cord dysfunction, physiotherapy for breathing pattern disorder, psychology (accessed via the primary care), and dietetics.(27, 28)

Final clinical review was undertaken six months after initial assessment. Baseline and follow up doses of inhaled and oral corticosteroids, biologic asthma medications, FEV₁% predicted, and BMI were recorded. Due to the seasonal nature of asthma response in the four domains of symptoms, quality of life, exacerbations and lung function were also analysed according to season of enrolment. Ethics approval was obtained for this study from the Institutional Human Research Ethics Committee (Reference 285/15).

Statistical methods

Response to systematic assessment was compared between baseline and six-month review. Patients were excluded from analyses if they did not have paired baseline or follow up asthma control, quality of life or exacerbation data. Response was defined by the minimum clinically important difference (MCID) for the ACQ6 (≥ 0.5)(29), and AQLQ (≥ 0.5)(30), any reduction in the number of exacerbations, and an increase in FEV₁ of greater or equal to 100mL between baseline and follow up.(31) Characteristics of responders versus non-responders were evaluated first with univariate analyses then multivariate analyses using logistic regression. Variables that were included in the logistic regression model were FEV₁

%predicted, age, sex, eosinophil count, and factors that had a p-value of <0.2 on univariate analysis. Statistical significance was set at a p-value of <0.05. Data was analysed with SPSS Version 24 (IBM, Armonk, NY).

Results

Demographics

In total 163 patients underwent systematic assessment during the specified time period and their baseline characteristics are shown in *Table 1*. Two patients were excluded from analysis due to loss to follow-up and resulting lack of outcome data in all domains. Patients with incomplete follow up data were excluded from the relevant analyses. 97% of patients had an underlying diagnosis of asthma (*Table 1*) with only 5 patients misdiagnosed with asthma prior to referral. Not all patients met a diagnosis of severe asthma as per ERS/ATS criteria but all patients had factors which meant their asthma was poorly controlled on referral for the assessment

Overall response

Among the entire cohort, between the initial and six-month assessments, mean number of exacerbations reduced from 2.5 to 1.2 ($n = 153$, $p < 0.001$), mean ACQ reduced from 2.4 to 1.9 (lower score indicates better control, $n = 153$, $p < 0.001$), mean AQLQ increased from 4.2 to 4.8 (higher score indicates better quality of life, $n = 153$, $p < 0.001$), and mean FEV₁ from 1.98 litres to 2.1 ($p = 0.002$).

Overall control

At baseline 95% (154/163) of patients met criteria for having uncontrolled asthma (those with one or more of: ACQ ≥ 1.5 , ≥ 2 severe exacerbations or ≥ 1 serious exacerbation (requiring hospitalization, intensive care admission or mechanical ventilation), FEV₁ <80%).

At follow up 79% of patients (128/163) met criteria for having uncontrolled asthma in one or more domain, an improvement of 16%. At follow up overall 59% still had an FEV₁ <80%, 64% had ACQ ≥ 1.5 and 31% were uncontrolled with regard to exacerbations.

Characteristics of those uncontrolled at follow up (% total or mean $\pm$ SD): 65% female, age 52 $\pm$ 14 years, duration of asthma 32 $\pm$ 19 years, BMI 31 $\pm$ 8 kg/m², FEV₁ 62 $\pm$ 21 %predicted. The factors that were significantly associated with being uncontrolled compared to controlled at follow up were FEV₁ %predicted (62 versus 84%predicted, $p < 0.001$), baseline ACQ (2.5 versus 1.8, $p = 0.006$), and number of new comorbidities diagnosed (2.7 versus 2, $p = 0.02$).

When the 12 patients commenced on biologics between initial and six-month assessments were excluded, improvements in asthma outcomes remained statistically and clinically significant; mean number of exacerbations: 2.4 to 1.1 ($p < 0.001$), mean ACQ: 2.4 to 1.9 ($p < 0.001$), mean AQLQ: 4.2 to 4.8 ($p < 0.001$), and mean FEV₁ from 2 to 2.1 litres ($p = 0.03$).

Responder analysis

Of 161 patients, 140 (87%) improved in at least one of four domains. 98/153 (64%) had reduced exacerbations, 83/153 (54%) had an ACQ score improvement ≥ 0.5 , 82/153 (54%) had an AQLQ score increase ≥ 0.5 , and 59/146 (40%) had an improvement in $FEV_1 \geq 100$ ml (*Figure 1*). When stratified according to season of baseline review there was no significant difference in the number of responders in the domain of exacerbations ($p=0.2$), ACQ ($p=0.4$), AQLQ ($p=0.4$) or FEV_1 ($p=0.7$).

Responder overlap

The overlap in improvement between domains is represented in *Figure 1*. Of 161 patients; 14 patients (9%) improved in all four domains, 49 patients (27%) improved in three domains, 42 (26%) improved in two domains and a further 35 patients (22%) improved in one domain. The last group tended to show improvements in either exacerbation rate or lung function rather than quality of life or asthma control (*Figure 1*). Twenty-one patients (13%) had no improvement in symptom control, quality of life, exacerbations or lung function.

Response predictors

Exacerbations

The number of exacerbations was reduced in 98 patients (64%), did not change in 29 patients [19%, including 18 (12%) who had no exacerbations prior to or during follow up] and increased in 26 patients (17%, *Figures 1 and 2*). Of the 29 patients who had the same number of exacerbations before and after systematic assessment, 10 had an improvement in both asthma control and quality of life, four had an improvement in either control or quality of life and 11 had an improvement in neither (with four missing quality of life and asthma control data at follow up). On univariate analysis, factors that were significantly associated with an reduced number of exacerbations were the presence of depression and a higher number of exacerbations prior to initial visit (*Table 2*).

On multivariate analysis, factors that were independently associated with a reduction in asthma exacerbations were female sex, a higher number of exacerbations at baseline, a higher baseline Berlin score and depression (*Table 3*).

Asthma control

Patients who had a significant improvement in asthma control tended to be female (66%) with mean age 52 ± 14 years, with no other difference in demographics between responders and non-responders. On univariate analysis the factors that were significantly associated with an improvement in asthma control were poorer asthma control at baseline, poorer quality of life at baseline, higher reliever use over the past seven days (41 actuations versus 20, $p = 0.006$), and the presence of atopy (*Table 2*).

On multivariate analysis, factors that were independently associated with improved asthma control were poorer baseline asthma control and asthma-related quality of life (*Table 3*).

Quality of life

Patients with significantly improved quality of life were more likely to be female (73% versus 52%, $p=0.007$) with mean age of 51 ± 15 years. Factors that were significantly associated with an improvement in AQLQ on univariate analysis were female sex, absence of OSA, poorer quality of life at baseline, a shorter duration of asthma, and allergic rhinitis symptoms (*Table 2*).

On multivariate analysis, female sex, poorer baseline quality of life, and presence of baseline allergic rhinitis symptoms were independently associated with improved quality of life (*Table 3*).

Lung function

Factors that were associated with an improvement in FEV_1 on univariate analysis were lower FEV_1 at baseline, presence of atopy, absence of anxiety, higher reliever use over 7 days and better asthma control at baseline (*Table 2*).

On multivariate analysis, factors that were independently associated with improvement in FEV_1 were lower baseline FEV_1 %predicted and anxiety (*Table 3*).

Corticosteroid burden

Inhaled corticosteroids

There was no difference in inhaled corticosteroid dose between baseline and follow up (1789mcg versus 1788mcg, $n = 160$, $p=0.98$).

Oral corticosteroids

Of 163 patients, 46 (28%) were on oral corticosteroids at baseline with a mean dose of 11 ± 10 mg. Of these 46 patients, 19 had ceased oral corticosteroids completely by follow up, but four additional patients initiated oral corticosteroids during the assessment period, giving 31 (19%) on oral corticosteroids at follow up. There was a significant reduction in oral corticosteroid burden between baseline and follow up both overall (3.3mg versus 1.7mg, $n=160$, $p=0.003$) and amongst only those who were taking oral corticosteroids at baseline (11mg versus 5mg, $n=46$, $p < 0.001$, *Figure 3*).

Biologic use amongst this cohort was uncommon; nine patients (6%) were on biologics at baseline and a further 12 patients (7%) were initiated on biologics during the assessment period. Of the 12 patients who initiated biologics during the assessment period, seven were on baseline corticosteroids with a mean dose of 8.4mg. After systematic assessment four of these were able to stop corticosteroids reducing the mean oral corticosteroid dose in this group to 3.6mg.

After excluding the seven patients on oral corticosteroids at baseline who commenced monoclonal biologics during the assessment period, there remained a large and statistically significant reduction in oral corticosteroid dose between baseline and follow-up from 11mg to 5.6mg ($p=0.001$, *Figure 3*).

Other management

Optimisation of asthma treatments during the treatment period included: 20% had increased inhaled corticosteroid (ICS)/long acting beta agonist (LABA) combination inhalers,

23% initiated small particle ICS, 9% initiated long acting muscarinic antagonist (LAMA), 2.5% initiated a macrolide, and 10% initiated a leukotriene receptor antagonist. All patients underwent intensive education on medication adherence, inhaler technique and self management strategies. Additionally 41% had an electronic adherence monitor fitted.

Comorbidities

A mean of 2.5 ± 1.5 comorbidities were diagnosed in each patient (*Figure 4*). There was no significant difference between the mean change in ACQ (0.5 versus 0.4, $p=0.5$), AQLQ (0.6 versus 0.6, $p=0.9$), exacerbations (1.4 versus 1.3, $p=0.9$), FEV₁ in mL (100 versus 70, $p=0.6$), or oral steroid reduction (5 versus 2.5mg, $p=0.3$) in those who had more or less than the mean comorbidities diagnosed.

Non responders

Complete non-responders in all four domains had a mean duration of asthma of 34 years, 84% were of high socioeconomic status, smoking status: 65% never, 29% ex-smoker, and 6.5% current smokers; and 57% were employed. Mean blood eosinophils were $0.3 \times 10^9/L$, FeNO 29 parts per billion, IgE 448 kU/L, and they had fewer exacerbations at baseline (1.65 Vs 2.75, $p=0.008$) less OCS (1.4 Vs 3.7mg $p=0.02$), but similar ICS (1859mcg) doses at baseline compared to responders.

In terms of comorbidities: 53% had chronic cough, 52% allergic rhinitis, 48% atopy, 39% chronic rhinosinusitis, 13% confirmed vocal cord dysfunction, 23% dysfunctional breathing, 39% obesity (mean BMI 29), 29% OSA, 35% depression (HADS D), 21% anxiety (HADS A), 55% childhood onset, 12% COPD, 39% GORD, and 40% dysfunctional breathing (on Nijmegen score). These comorbidity rates were similar to those amongst responders.

Discussion

Main findings

We confirm previous data supporting clinical benefit with systematic assessment for severe asthma, by demonstrating overall improvements in symptom control, quality of life, exacerbation rates and airflow obstruction regardless of whether patients received monoclonal biologics. Responder analysis, undertaken for the first time, also revealed that most patients demonstrate a clinical response following systematic assessment with improvement in at least one domain found in 87% of patients; reduced exacerbations in 64%, improvements in ACQ6 and AQLQ reaching or exceeding the minimal clinically important difference (MCID) in 54% for each measure, and a 100 ml or greater increase in FEV₁ in 40%. Importantly, overall oral corticosteroid burden was halved at six months, with benefits extending even to patients *not* commenced on monoclonal biologics.

Interpretation and implications

To our knowledge, this is the first responder analysis of systematic assessment for severe asthma. Our analyses show that systematic assessment was beneficial in the majority of our patients, with 87% of the cohort improved in at least one domain. No single outcome was sufficient to assess patient response to interventions, and a combination of measures remains necessary in this area. There were varying proportions of responders for each domain assessed. Most patients (64%) experienced a reduction in exacerbations, with a further 12% remaining exacerbation-free during the six-month assessment period. A smaller proportion (54%) met the MCID for improvements in symptom control and quality of life respectively. Fewer still (40%) experienced a 100ml or greater improvement in FEV₁.⁽³¹⁾

Overlap between domain responses was limited, as demonstrated in figure 2. Intriguingly, the degree of overlap between domain outcomes was not uniform – improvements in asthma control or asthma-related quality of life were almost always accompanied by corresponding improvements in other domains, but overall 14% of patients had an improvement in exacerbations and 7% an improvement in lung function without improvements in other domains (Figure 1).

The second major focus of this study was to determine whether a patient's response to systematic assessment was predictable from their baseline characteristics. There were few reliable predictors of response on multivariate analysis. Female sex, allergic rhinitis and depression appeared to have minor predictive value for improvement in different domains, and the latter two may represent treatable traits amenable to specific therapies.⁽²⁾ There was an inconsistent effect for sleep apnoea, which predicted less improvement in AQLQ but (at least as measured by the Berlin score) a greater reduction in exacerbation rate. Poorer baseline asthma status was the most consistent predictor of response across domains. A possible explanation for this is regression to the mean, which can confound results of uncontrolled studies such as ours. Against this, however, is the magnitude of improvement in ACQ and AQLQ in our cohort, which were substantially larger than occurred in the purely observational but otherwise comparable Australasian Severe Asthma Network registry, which recruited participants with asthma of similar severity.⁽³²⁾

The final question in this study was to examine the effect of systematic assessment independent to the provision of severe asthma monoclonal biologics, in an era where

effective type 2 therapies have entered clinical practice. Reassuringly, there were significant improvements in all domains even after excluding patients commencing monoclonals during the assessment period. This finding is particularly relevant for those severe asthma patients who are not eligible for monoclonal therapies due to their asthma.

Of note, we also found a 49% reduction in oral corticosteroid burden in patients who had not commenced monoclonal biologics during systematic assessment. This corticosteroid dose reduction is similar in magnitude to that achieved by monoclonal biologic therapy in randomised trials. A previous study of systematic assessment published prior to the era of severe asthma monoclonal biologics had found improved asthma outcomes but at the expense of *greater* oral corticosteroid burden.(4) After the entry of monoclonal biologics into clinical practice, a second study from the same network demonstrated a reduction in oral corticosteroid dose following systematic assessment, but this may have represented the therapeutic effect of those same biologics.(8) In our study, we show a reduction in the number of patients requiring maintenance oral corticosteroids (by a third), and a substantial reduction in dose (by about half) even *after* excluding patients commenced on monoclonal biologics. This suggests an additional and substantial corticosteroid-sparing effect just from undergoing systematic assessment alone. Systematic assessment may therefore be of particular value to patients who are *not* eligible for monoclonal biologics, as the outcome benefit is similar to that seen with these medications.

Our results also suggest that the benefit of systematic assessment for severe asthma is conferred by more than just improved pharmacological targeting of severe asthma biology. Additional value likely lies in the multi-dimensional evaluation and optimisation of various key issues such as medication use and adherence, patient understanding and self-management, and relevant triggers and comorbidities

Limitations

This study is subject to the usual biases attending an uncontrolled observational study design, including regression to the mean as already discussed. Additionally, as asthma control fluctuates, the results may have been biased by limited follow up duration; we did not assess response beyond six months. Because systematic assessment has become the gold standard in the management of severe asthma it becomes difficult to perform a randomised study, but without a control arm we acknowledge that we cannot be certain that improvements came about due to systematic assessment. We also did not assess response beyond six months. In our cohort, the rates of monoclonal biologics commencement were low; for much of the study period, mepolizumab and benralizumab were not available, and government reimbursement for all monoclonal therapy required 12 months of prior specialist care. During systematic assessment, multiple concurrent interventions were offered according to protocol, so it remains unclear which aspects of management are the most (cost-)effective.

Conclusion

Our study suggests that systematic assessment for difficult asthma is beneficial for most such patients, with few reliable predictors of response. A third of patients requiring maintenance oral corticosteroids may be able to cease oral corticosteroids completely

following systematic assessment, with a halving of oral corticosteroid burden independent of monoclonal biologics.

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Tables:

Table 1: Baseline characteristics of patients who underwent systematic assessment for severe asthma.

Characteristic:	
Age (mean $\pm$ SD)	52 $\pm$ 14
Female sex	66% (107/163)
Pre bronchodilator FEV ₁ % predicted (mean $\pm$ SD)	67% $\pm$ 23
Final diagnosis asthma	97% (157/162)
FEV ₁ reversibility	60% (97/162)
PEF variability	14% (22/162)
AHR	12% (19/162)
Other	9% (14/162)
Duration of asthma, years (mean $\pm$ SD)	30 $\pm$ 19
Smoking history	
Never	56% (92/163)
Ex	39% (64/163)
Current	4% (7/163)
Low socioeconomic status	26% (43/163)
Inhaled corticosteroid dose (budesonide equivalent, mcg) (mean $\pm$ SD)	1791 $\pm$ 1004
Atopic	58% (95/163)
Eosinophil count (mean $\pm$ SD)	0.34 $\pm$ 0.35
FeNO (mean $\pm$ SD)	32 $\pm$ 27
IgE (mean $\pm$ SD)	500 $\pm$ 993
Number of exacerbations in prior 6 months (mean $\pm$ SD)	2.5 $\pm$ 2
ACQ6 (mean $\pm$ SD)	2.4 $\pm$ 1.3
AQLQ (mean $\pm$ SD)	4.2 $\pm$ 1.3

BMI (mean $\pm$ SD)	31 $\pm$ 8.3
Obesity	52% (85/163)
Allergic rhinitis	47% (76/163)
Chronic rhinosinusitis	60% (98/163)
Gastroesophageal reflux disease	46% (75/163)
Obstructive sleep apnoea	31% (51/163)
Anxiety	26% (43/163)
Depression	30% (49/163)
Dysfunctional breathing	41% (67/163)
Vocal cord dysfunction (on scope)	16% (26/163)
Vocal cord dysfunction (scope or clinical)	36% (59/163)
Monoclonal biologic at baseline	6% (9/163)
New biologic during assessment period	7% (12/163)

SD – standard deviation

FEV1 – Forced expiratory volume in one second

PEF – Peak expiratory flow

AHR – Airway hyperresponsiveness

FeNO – Fractionated exhaled nitric oxide

IgE – Immunoglobulin E

ACQ6 – Asthma control questionnaire 6

AQLQ – Asthma quality of life questionnaire

BMI – Body mass index

Table 2: Factors associated on univariate analysis with an improvement in asthma control (ACQ6 improvement ≥ 0.5), asthma-related quality of life (AQLQ improvement ≥ 0.5), number of exacerbations and FEV₁ (improvement ≥ 100 mL)

Outcome	Variable	P value
ACQ6 improvement	Asthma diagnosis confirmed	0.18
	Obesity	0.19
	Asthma onset	0.095
	Atopic	0.04
	ACQ6 at baseline (higher)	0.00
	AQLQ at baseline (lower)	0.041
	Reliever use over 7 days (41 Vs 20, higher)	0.006
	RCAT (lower)	0.038
	GERQ (higher)	0.079
	Berlin (higher)	0.137

AQLQ improvement	Female sex	0.007
	OSA not present	0.004
	AQLQ baseline (lower)	0.11
	Duration of asthma (shorter)	0.085
	RCAT (lower)	0.005

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Improved exacerbations	Socioeconomic status (low)	0·071
	VCD clinical diagnosis	0·073
	Obesity	0·165
	Depression present	0·03
	Asthma onset (adult)	0·12
	Exacerbations in 6 months prior to V1 (higher)	0·000
	Total ICS daily dose (lower)	0·17
	GERDQ (higher)	0·2
	Berlin (higher)	0·17
Improved FEV₁	Male sex	0·08
	Allergic rhinitis (present)	0·11
	Chronic rhinosinusitis (present)	0·14
	Atopy (present)	0·02
	Unemployed	0·14
	Anxiety (not present)	0·04
	FEV₁ %predicted at baseline	<0·001
	Blood eosinophils	0·12
	Reliever use over 7 days	0·01
	Total ICS daily dose	0·18
	ACQ6 baseline (higher)	0·04
	AQLQ baseline	0·1

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692 ACQ6 – Asthma control questionnaire 6

693 AQLQ – Asthma quality of life questionnaire

694 FEV₁ – Forced expiratory volume in one second

695 VCD – Vocal cord dysfunction

696 V1 – Visit 1

697 ICS – inhaled corticosteroids

698 GERDQ – Gastroesophageal reflux disease questionnaire

699 RCAT – Rhinitis control assessment test

700 OSA – Obstructive sleep apnoea

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702

703 **Table 3:** Multivariate analysis showing factors independently associated with an
 704 improvement in asthma control, asthma-related quality of life, exacerbations and FEV₁ after
 705 systematic assessment for difficult asthma.

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		Odds Ratio	Significance
ACQ6	Initial ACQ6	0·31	0·000
improvement	Initial AQLQ	0·53	0·024
AQLQ	Female sex	3·73	0·014
improvement	RCAT	1·1	0·021

	OSA not present	4.8	0.001
Exacerbation	Female sex	0.33	0.036
improvement	Baseline exacerbation rate	0.38	0.000
	Berlin score	0.57	0.033
	Depression	0.36	0.05
FEV₁	Baseline FEV ₁ %pred	1.03	0.008
improvement	Anxiety	0.27	0.02

FEV₁ – Forced expiratory volume in one second
ACQ6 – Asthma control questionnaire 6
AQLQ – Asthma quality of life questionnaire
RCAT – Rhinitis control assessment test
OSA – Obstructive sleep apnoea

Figures:

Figure 1: Overlap of responders to different asthma outcomes after systematic assessment; Asthma-related quality of life based on Asthma control based on Asthma Control Questionnaire 6 improvement of ≥ 0.5 (orange), Asthma Quality of Life Questionnaire improvement of ≥ 0.5 (red), improved number of exacerbations (green), improvement in FEV₁ of $>100\text{mL}$ (blue).

Figure 2: Waterfall plot of clinical response in the domains of exacerbations, asthma control, asthma-related quality of life and FEV₁%predicted in those undergoing systematic assessment for asthma.

Figure 3: Change in dose of oral corticosteroid dose between baseline and follow up after systematic assessment for difficult asthma. Panel A overall ($p < 0.001$), Panel B those started on a new asthma monoclonal during the follow up period, Panel C those who did not start a biologic during the follow up period ($p = 0.001$). Panel D: Reduction in dose of oral corticosteroids (in mg) amongst those on oral corticosteroids at baseline or who started oral corticosteroids during the assessment period.

Figure 4: Number of new comorbidities diagnosed during systematic assessment.

