

INVITED REVIEW SERIES: HOW TO SET UP PULMONARY SUBSPECIALTY SERVICES

How to set up a severe asthma service

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ABSTRACT

Severe asthma affects 5–20% of the asthma population but is discordantly responsible for the major burden of illness and impairment to quality of life. Patients with severe asthma continue to experience ongoing symptoms despite maximal therapy. A severe asthma service

provides a systematic approach to the management of the disease and aids in confirming the correct diagnosis, managing comorbid conditions that may mimic or aggravate asthma, and provides the environment to optimize treatment and asthma self-management skills and education. A severe asthma service is also the ideal environment for trialling add-on therapies and hence can improve patient outcomes and clinical practice. Within such a service there are many opportunities for training and research. In this article we describe the purpose of a severe asthma clinic, the necessary components of a service including staffing and facilities and the processes for trialling additional therapies used in the management of severe asthma.

Key words: asthma, clinical respiratory medicine, eosinophil.

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INTRODUCTION

Asthma is responsible for a large and increasing burden of illness in Australia.¹ Much of the cost and resources required to effectively manage asthma are expended upon a small group of people with severe disease whose poor control persists despite maximal treatment. Key characteristics of this population are the high burden of illness despite maximal pharmacotherapy, the heterogeneous nature of the problem and its associated comorbidities, and the significant social, psychological and economic impact of severe asthma.² Consequently, people with severe persistent asthma require a different management approach that addresses these issues. There is an additional need for research into new treatment strategies for severe persistent asthma.

Organization of care for people with severe asthma requires multidisciplinary coordination and management. Specialized asthma centres are an effective way to deliver this care. These centres confirm the diagnosis, optimize the treatment and self-management skills, minimize and manage potential side-effects of therapy, offer participation in trials of add-on therapies and new anti-asthmatic medications and provide

Table 1 Severe asthma clinic aims and structured approach to management

Confirm diagnosis	Objective confirmation of increased variability of airflow
Optimize self-management skills and treatment	Knowledge, inhalation device technique, written action plan, medication adherence, self-monitoring
Assess and treat asthma triggers and relevant comorbidities	Smoking VCD, OSA, rhinosinusitis COPD, bronchiectasis Anxiety, depression GORD, obesity, osteoporosis
Consider and possibly trial add-on therapies as appropriate	Parenteral corticosteroids Omalizumab Itraconazole Macrolide antibiotics Immunosuppressives
Provide opportunities for training and research	

GORD, gastro-oesophageal reflux disease; VCD, vocal cord dysfunction.

continuous education to people with difficult asthma (Table 1).²⁻⁵ This review details these processes for the management of severe asthma.

ESTABLISHING A SEVERE ASTHMA SERVICE

What type of patients can benefit?

Asthma is a common condition that can usually be controlled by accessible pharmacotherapy and asthma self-management education to teach the skills necessary to manage the disease. However, a small percentage of people diagnosed with asthma continue to experience manifestations of the disease despite optimal therapy.³ This puts them at risk of exacerbations, loss of lung function and adverse effects of treatment. It is estimated that between 5% and 20% of adults with asthma have severe disease.^{6,7}

The definition of severe asthma that warrants referral to a severe asthma service is a person with diagnosed asthma, prescribed maximal inhaled therapy consisting of inhaled corticosteroid and a second controller (e.g. long-acting β_2 agonist), who continues to exhibit poor control, defined as persistent symptoms, frequent and/or life-threatening exacerbations, or persistent airflow obstruction. The service is also appropriate for people with asthma who require oral corticosteroid to maintain control.

Purpose of a severe asthma service

The purpose of a severe asthma service is multifactorial and progress through such a service should follow a staged and systematic approach to:

- Confirm diagnosis
- Optimize self-management skills and treatment
- Treat asthma triggers and relevant comorbidities
- Trial add-on therapies
- Provide opportunities for training and research

Confirm diagnosis (Table 1)

Misdiagnosis and symptom misattribution can confound the assessment of severe asthma. For these reasons, objective confirmation of a diagnosis of asthma is necessary. This can be made by demonstration of increased variability of airflow during expiration, which is the defining characteristic of asthma. The tests which achieve this are: assessments of bronchodilator responsiveness using pre- and post-bronchodilator spirometry, airway hyperresponsiveness using challenge agents including hypertonic saline, mannitol or methacholine, and variability of airflow over time measured by serial spirometry or peak expiratory flow readings.

Once a diagnosis of asthma is confirmed it is then important to identify other aggravating or coexisting factors that may complicate asthma management. Symptom misattribution occurs when a condition coexists with asthma and causes symptoms that mimic asthma. Common coexisting conditions that mimic or aggravate asthma are: vocal cord dysfunction (VCD), COPD, bronchiectasis, OSA, rhinosinusitis, obesity, anxiety and depression.⁸ Systematic assessment, identification and management of these conditions are necessary before increasing asthma pharmacotherapy.

Optimize self-management skills and treatment

Many patients have poor asthma management skills,^{9,10} and when these are optimized, then control of asthma can be re-established.¹¹ The key asthma management skills targeted in a severe asthma service are: inhaler technique, medication adherence, self-monitoring, written action plan (WAP) and knowledge. Studies investigating inhaler technique show that this skill requires frequent reinforcement,¹² at least each 3–6 months.

In an evaluation of 70 consecutive patients referred to the John Hunter Hospital's severe asthma clinic, only 60% of patients had adequate knowledge and only 34% had recalled being prescribed a written asthma action plan for exacerbations of their asthma. Furthermore, only 41% had previously undergone an asthma self-management and education programme. Once referred to the severe asthma clinic and following assessment and correction of asthma self-management skills and the provision of education, 22% achieved adequate control of their asthma and did not require any further treatment.¹³ These data demonstrate the importance of optimizing asthma management and skills early in the assessment of patients with severe asthma.

Inhaler technique

Inhaled medication therapy is integral to the management of severe asthma. Steps for correct inhalation technique for a range of devices can be found at <http://www.nationalasthma.org.au/content/view/548/984/>. Despite effective pharmacological therapies, the control of symptoms in diseases such as asthma remains poor.^{14,15} Ineffective inhalation technique leads to insufficient dosing and may contribute to poor symptom control.

Dry powder inhalers are frequently prescribed to treat asthma. The key to successful therapy with dry powder inhalers, however, is dependent on the patient's ability to generate sufficient inspiratory flow to disperse the medication to the optimal particle size for pulmonary deposition.¹⁶ Unfortunately, there are a number of patient groups who have difficulty achieving sufficient inspiratory flow, in particular those with severe airflow obstruction.^{16,17} It is necessary to ensure patients with severe asthma are able to adequately generate enough inspiratory flow to activate the device they are prescribed.

In recent years there has been a progressive increase in the types of inhalation devices used in asthma. This can lead to inhaler device polypharmacy, a situation where an individual uses multiple types of inhalation devices to deliver their medications. We have demonstrated that this is a common problem among adults with asthma and that inadequate inhalation device technique is also common, especially among patients using three or more delivery devices. Inhaler device polypharmacy can lead to poor asthma control through inadequate delivery of medication¹⁸ and is more likely to occur in patients with severe disease. As treatment is escalated in severe asthma, this population becomes increasingly at risk of inhaler device polypharmacy and therefore inadequate inhaler device technique. Reassessment of inhaler technique and regime complexity is necessary irrespective of the duration since diagnosis or frequency of health-care utilization.

Self-management education is recommended in clinical practice guidelines¹⁹ as an integral part of asthma management. Systematic reviews have been conducted for self-management and for integrated disease management in asthma.¹¹ In a Cochrane systematic review of asthma self-management education in adults, 36 randomized controlled trials that compared self-management education to usual medical care were evaluated. The results of this analysis demonstrated that self-management education reduced hospitalizations, emergency department visits, unscheduled visits to the doctor, days off work or school, nocturnal asthma and improved quality of life. The conclusions drawn from this review indicate that education in asthma self-management which involves, the provision of information, self-monitoring by either peak expiratory flow or symptoms, regular medical review coupled with a written asthma action plan improves health outcomes for adults with asthma.¹¹ Whilst patients with severe asthma often have long-standing disease, self-management skills and knowledge in this

population remains a problem¹³ and optimization of these skills is necessary regardless of the duration of asthma.

Written action plans

A WAP is a set of written instructions that helps people with asthma detect early signs and symptoms of an exacerbation and provides instructions about how to manage these exacerbations. The plan should include instructions for maintenance therapy, early exacerbation management and crisis management.^{20,21} WAP are essential to effective self-management in asthma,¹¹ and their prescription is a key recommendation of international clinical practice guidelines for asthma.^{19,22} Regular review and update of WAP in patients with severe asthma can be achieved in the severe asthma clinic.

Adherence

Adherence is poor in many diseases, including asthma,²³ and it is essential that adherence is assessed to determine whether this is contributing to poor disease control in severe asthma. Studies in severe asthma that use objective measures of adherence observe that one in three patients who were referred for assessment of their severe asthma had filled <50% of their prescriptions for inhaled combination therapy and 88% admitted poor adherence to regular pharmacotherapy.²⁴

Methods to assess non-adherence in severe asthma require non-judgemental interviewing techniques and assessment of the reasons for the missed doses, such as intentional non-adherence, unintentional dose loss or a combination of both. There is also a need to develop better methods to objectively assess adherence and to design effective interventions for non-adherence in severe asthma.

Treat asthma triggers and comorbidities (Table 2)

There are several comorbid conditions that require assessment in patients with severe asthma. Some of these conditions are relevant because they can lead to symptom misattribution or impaired quality of life. These include: VCD, COPD, bronchiectasis, OSA, rhinosinusitis, obesity, gastro-oesophageal reflux disease (GORD), anxiety and depression. Others are relevant as a complication of severe asthma, such as allergic bronchopulmonary aspergillosis, COPD, anxiety and depression. Others may develop as a consequence of therapy for severe asthma, such as osteoporosis, obesity and diabetes mellitus.

It is also important to identify and assess relevant trigger factors in patients with severe asthma. Triggers include allergen exposure, occupational chemical

Table 2 Relevant comorbidities in severe asthma

Comorbidity	Symptom misattribution	Complication of severe asthma or its treatment
Smoking	Yes	No
Rhinosinusitis	Yes	No
Vocal cord dysfunction	Yes	?
OSA	Yes	No
COPD	Yes	Yes
Bronchiectasis	Yes	Yes
Anxiety, depression	Yes	Yes
Obesity	Yes	Yes
Osteoporosis	No	Yes
GORD	Yes	No

GORD, gastro-oesophageal reflux disease.

Table 3 Treatment options based on inflammatory phenotype

Inflammatory phenotype	Treatment options
Eosinophilic bronchitis	ICS/LABA: adherence LTRA: add-on montelukast Maintenance OCS: dose adjustment by sputum eosinophils Immunosuppressives: oral gold/methotrexate Parenteral steroid Anti-IL-5*
Non-eosinophilic bronchitis	ICS/LABA Address Triggers: Smoking Infection Macrolide: clarithromycin 250 mg daily for 16 weeks Theophylline Anti-TNF α *
Elevated IgE	Omalizumab Itraconazole for ABPA and fungus associated asthma

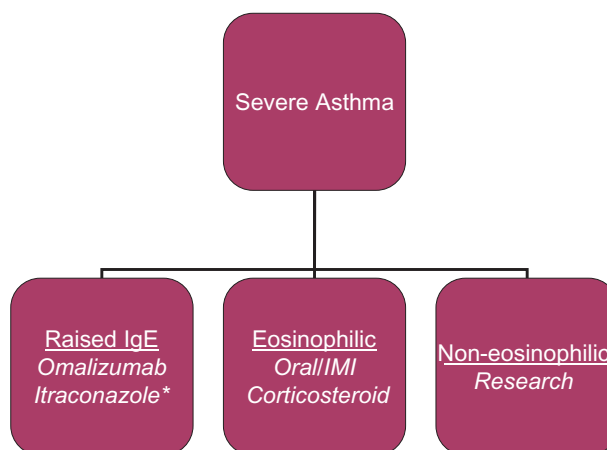
* Indicates research option, experimental treatments, or restricted to use in clinical trials.

ABPA, allergic bronchopulmonary aspergillosis; ICS, inhaled corticosteroid; LABA, long-acting β agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; TNF, tumour necrosis factor.

exposure, tobacco smoking and frequent infections. Removal of these factors can lead to improved asthma control.

Trial add-on therapies for asthma (Table 3)

A range of therapeutic options are available to manage patients with severe asthma. A severe asthma clinic can be used to coordinate the delivery and

**Figure 1** Management of severe asthma according to inflammatory phenotype. The key treatment options are shown in the figure, with more detailed selections in Table 3. *If fungal sensitization is present. IMI, intramuscular injection.

response evaluation to these therapies. An emerging approach in many centres is to select add-on therapies according to asthma phenotype (Figure 1, Tables 3,4).^{25,26} This approach requires that objective measures of airway inflammation be applied.

Training opportunities

The structured multidisciplinary approach used in a severe asthma clinic offers high quality training opportunities for a range of health-care professionals including basic training physicians, advanced trainees, nurses and speech pathologists. These personnel can then translate the skills gained in a severe asthma clinic into their usual clinical practice.

SET-UP

The set-up and initiation of a severe asthma service can be facilitated by a business case that highlights the potential for reduced asthma exacerbations and quality use of medicines. Successful achievement of these goals can be expected to lead to better patient care and more efficient use of health-care resources. It is now well established that patients with severe asthma require considerable health-care resources to manage their condition. This resource use arises due to frequent exacerbations leading to increased hospitalizations, and the requirement for expensive and/or toxic pharmacotherapy. A severe asthma service can be expected to reduce hospitalization for asthma exacerbations. The service can also be used to monitor and control the use of expensive drugs, thus leading to better use of medication.

Referral is facilitated by the structure of the service which provides patients and referring clinicians with access to specialized services. These can include multidisciplinary assessment and management,

Table 4 Matrix of severe asthma phenotypes and targeted treatments

	Speech therapy	Diet	LTRA	OCS/IM CS	Macrolide	Itraconazole	Omalizumab	Tiotropium	Methotrexate/gold	IL-5
Asthma/UAD										
Obese asthma										
ASA										
Eosinophilic										
Non-eosinophilic (Neutrophilic/PGA)										
Aspergillus-sensitive										
IgE-mediated										
Fixed AFO										

The shaded areas represent the potential treatments for the severe asthma phenotypes.
AFO, airflow obstruction; ASA, aspirin sensitive asthma; IM CS, intramuscular corticosteroid; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PGA, paucigranulocytic asthma; UAD, upper airway dysfunction.

objective assessment using inflammometry, access to restricted pharmacotherapies, and opportunities to trial new medications in a research setting. In a catchment area of 350 000 people, we find that a severe asthma service that runs two sessions per month can manage the illness burden. Initial patient loads of 20 per year were sufficient to initiate the service, which will then expand to approximately 80 patients per year.

STAFFING: MULTIDISCIPLINARY TEAM AND THEIR ROLES

A multidisciplinary severe asthma service offers the best approach in dealing with the disease, its comorbidities and complications of management and self-management skills. We consider the core personnel required to run a severe asthma clinic to be a respiratory physician, specialist nurse, pulmonary function scientist and speech pathologist. With this level of staffing referral options are necessary to other health disciplines including psychology, dietetics, sleep services, pharmacist, otolaryngology and gastroenterology services (Table 5). The optimum staffing of a severe asthma clinic would include access to all of these services.

Medical

A respiratory physician with extensive experience in the management of severe asthma is required. The physician plays an essential role in the confirmation of an asthma diagnosis, assessment and management of aggravating factors and comorbidities, and ongoing treatment decisions for add-on therapies. Either training in sleep medicine or access for referral to a sleep physician is necessary.

Nursing

A nurse specialist with high level clinical skills and experience in chronic disease self-management and asthma management and education is integral in the assessment of control through symptoms, lung function and peak flows and in the ongoing management of severe asthma patients. They have the opportunity to provide education, assess and correct skills including inhaler technique, commence and review self-monitoring and reinforce the written asthma action plans. The nurse can assess and monitor adherence and smoking status and provide advice on adherence aiding strategies, trigger management and avoidance strategies including the provision of intensive smoking cessation counselling.
Another important role of the nurse in the severe asthma clinic is the monitoring of patients during treatment trials and the administration of supervised add-on therapies such as omalizumab or triamcinolone. The nurse should be adequately trained and skilled in anaphylaxis management and the delivery

Table 5 Staff and facilities required for a severe asthma service

Purpose	Staff	Facilities
Confirm diagnosis	Respiratory physician Pulmonary function scientist Radiographer	Clinic PF laboratory Medical imaging
Optimize treatment and self-management	Respiratory physician Nurse specialist	Clinic Placebo inhalation devices, peak flow meters, self-monitoring diaries, questionnaires
Treat asthma triggers and comorbidities	Pharmacy Respiratory physician Advanced trainee Nurse specialist Speech pathologist Dietitian Psychologist Sleep physician and technician Gastroenterologist Otolaryngology Physiotherapy	Measures of inflammation (FeNO, induced sputum, sputum processing) Clinic Drug administration clinic Rapid access clinic Sleep laboratory Thoracic radiology (high resolution CT) Facilities for aspirin sensitive asthma desensitization Epipen Sputum clearance devices

of patient education regarding anaphylaxis. The nurse can also provide rapid access and telephone support to patients under the care of the severe asthma clinic during exacerbations and in the presence of any adverse events.

Respiratory scientist

In addition to clinic-based spirometry, there are several pulmonary function assessments necessary for both confirming a diagnosis of severe asthma and in its ongoing management. An accredited pulmonary function laboratory and appropriately trained scientist is needed to perform lung volumes, gas diffusion studies, respiratory pressures, assessment of airways hyperresponsiveness, fraction of exhaled nitric oxide in exhaled breath (FeNO) and induced sputum protocols.

Speech pathologist

A speech pathologist with specialist skills in voice disorders is fundamental in a severe asthma clinic. The speech pathologist is responsible for assessing and treating patients with VCD and for managing patients with confirmed asthma who have coexisting dysphonia.

Dietitian

Obesity is a common and significant comorbidity in severe asthma.²⁷ The prevalence of asthma is increased by 50% in overweight/obese individuals and there is a dose-response relationship between body weight and asthma.²⁸ Obesity is also associated with increased asthma severity and decreased

response to treatment.^{29–31} Medications such as oral corticosteroids and inactivity related to breathlessness can exacerbate the rate of obesity in a severe asthma population. Weight loss has been shown to improve asthma symptoms and lung function.³¹ Access to a dietitian in a severe asthma clinic is needed to provide nutritional assessment and interventions to combat obesity. A further problem among severe asthma is glucocorticosteroid-induced osteoporosis. A number of studies conducted with premenopausal women have demonstrated a dose-dependent reduction in bone mineral density with inhaled corticosteroid use.^{32,33} Dietitians can also provide advice regarding dietary interventions for the prevention of bone mineral density loss.

Psychologist

Access to a psychologist for assessment and treatment of common conditions that coexist with severe asthma such as anxiety and depression is recommended. These services may be provided outside the severe asthma clinic provided assessment and treatment is available in a timely fashion.

Physiotherapist

There are several roles for a physiotherapist in a severe asthma service. These include: breath retraining for dysfunctional breathing; exercise training and pulmonary rehabilitation for coexisting COPD; and mucus clearance techniques for patients with mucus hypersecretion and also bronchiectasis.³⁴

Gastroenterologist

Access to gastroenterology services is important in severe asthma. GORD is common in patients with

severe asthma.⁸ GORD with proximal reflux can cause reflux laryngitis and symptom misattribution. Certain therapies for severe asthma can exacerbate GORD.

Administrative support

A severe asthma service should be supported by administrative assistance to facilitate the appointment scheduling, outpatient correspondence, scheduling of multidisciplinary meetings and ongoing assistance with quality improvement processes.

Multidisciplinary case review

A multidisciplinary case review meeting should be held as part of each clinic to review individual patient's progress and plan the next phase of care or intervention. These meetings make the most of the expertise of the individual team members and ensure a team-based approach. They can provide a learning environment for training clinicians and lead to improved outcomes for the patient.

FACILITIES

The physical environment required to conduct a severe asthma service includes a clinic equipped with consultation rooms for all of the members of the multidisciplinary team (medical, nursing, speech). Additionally, a suitable place to administer medications including omalizumab is necessary. This area should be equipped with basic life support equipment including adrenaline in the case of a medical emergency. The drug administration area should also be in close proximity to senior medical staff or a medical emergency team.

Rapid access and telephone support should be provided to patients within the severe asthma clinic to provide early intervention during acute exacerbations or in the case of adverse events related to treatment. This support can be provided by senior nursing staff and advanced trainees or registrars in consultation with the respiratory physician/s.

A Pulmonary Function Testing (PFT) Laboratory equipped in the measurement of lung volumes, gas diffusion studies, respiratory pressures, assessment of airways hyperresponsiveness, FeNO and induced sputum protocols should also be in close proximity to the clinic. Access to point of care FeNO measurements is necessary to guide treatment decision. In addition to the PFT Laboratory, access to a sputum processing laboratory for performing inflammatory cell counts is also needed.

A meeting room for multidisciplinary case review with access to the medical records is recommended.

Further services necessary for a severe asthma clinic can be co-located in the same hospital. These include facilities for radiology services for CXR and high resolution CT, a sleep laboratory/unit to conduct sleep studies and hospital pharmacy to dispense the

medications for the treatment trials, in particular the special access treatments such as omalizumab.

Equipment requirements are minimal but should include placebo inhaler devices to regularly assess technique, peak expiratory flow meters and peak expiratory flow and symptom monitoring diaries, asthma action plan templates and other patient education materials, including specific information brochures regarding the add-on therapies and speech therapy techniques. Access to sputum clearance devices may also be useful to treat people with excessive mucus hypersecretion. Systematic assessment protocols and processes for transition through the severe asthma clinics are also necessary. (Copies of protocols and education materials can be provided upon request to the authors). Table 5 highlights the facilities and staffing required in a severe asthma service.

DELIVERY

Patient selection and referral pathways

Patients should be referred to a severe asthma service by a respiratory or general physician. To ensure that the resources allocated to a severe asthma service are optimally utilized, a clear referral process is required. Referral by a respiratory or general physician will ensure that individuals have had a medical assessment and some initial optimization of asthma therapy. Referral to a severe asthma service is appropriate when a patient's symptoms persist despite maximal guideline-based therapy.

A referral form should be generated and made readily available to the referrers. Written consent to participate in a severe asthma clinic or to receive certain therapies may be a requirement in some situations or health-care systems. This can be obtained at the initial assessment or at initiation of those therapies.

Communication with the referring physician is essential for ongoing support of the programme. If the patient enters the programme, the referrer must be informed of the results of the baseline and ongoing assessments, in addition to the outcomes of any additional therapies. Furthermore, if a patient declines to participate, or is deemed not suitable for the severe asthma clinic, the referrer should be informed. Once asthma control and treatment is optimized, patients in the severe asthma clinic should be transferred back to their referring physicians. If ongoing treatment is necessary in the case of long-term omalizumab for example then this must be communicated with the referring physician and a follow-up plan negotiated with the referrer.

PATIENT ASSESSMENT

The patient assessment is multidisciplinary. The initial assessment involves a medical practitioner to assess the patient's history, confirm diagnosis and assess comorbidities and confounding diseases, as

well as optimize therapy. The history should include the frequency of severe asthma exacerbations and the number of hospitalizations and intensive care unit admissions. Also included is an assessment of environmental exposures including exposure to allergens, occupational agents, and chemicals/pollutants and a smoking history.² Important baseline investigations include lung function tests, serum IgE and peripheral blood eosinophil count, allergy skin tests and assessment of airway inflammation (FeNO, induced sputum). The involvement of other health professionals in the assessment then follows.

An asthma educator nurse specialist should assess and optimize asthma self-management skills and identify barriers to successful asthma management. They can perform an assessment of psychological status using screening questionnaires for anxiety and depression, such as the Hospital Anxiety and Depression Scale.³⁵ Asthma control and health status can be assessed using validated questionnaires such as the Juniper Asthma Control Questionnaire¹⁵ and the Asthma Quality of Life Questionnaire.³⁶

Speech pathology assessment involves clinical examination of VCD and dysphonia. The assessment involves case history, examination of VCD and cough symptoms, auditory perceptual analysis of voice, and clinical examination of pitch, loudness, breathing patterns, respiratory support for speech and extrinsic laryngeal muscle tension. It is also valuable to note whether the voice assessment tasks trigger cough and VCD symptoms. Instrumental examination of voice can also be beneficial but requires assessment in a separate speech laboratory. Patients with significant dysphonia are referred to the Voice Clinic for nasendoscopy which is staffed by otolaryngology and speech pathology.

TREATMENT

In severe asthma, inhaled corticosteroids and bronchodilators remain the cornerstone of therapy; however, as asthma severity increases, patients may become less responsive to these therapies or require more targeted treatment to achieve satisfactory asthma control. A severe asthma clinic provides the ideal setting to allow targeted treatment of difficult asthma based on asthma phenotypes (Tables 3,4). The use of individual trials in single patients can be a very powerful means of establishing the efficacy of a drug in a specific patient.⁵

Once maximal guideline-based therapy has been established, additional pharmacotherapies can be trialled if asthma control has not been achieved. Predicting response to treatment can be aided by establishing the asthma phenotype and targeting therapy to the problem. The matrix presented in Table 4 demonstrates the potential treatments and therapies used in a severe asthma clinic against the possible asthma phenotypes. Table 6 provides suggestions for the assessment, monitoring, follow up and safety considerations for many of the treatments used in a severe asthma service.

Corticosteroids: inhaled corticosteroid, oral corticosteroid, intramuscular

Treatment of severe eosinophilic asthma with high dose oral corticosteroids can result in clinically meaningful improvements.^{2,37} The use of sputum-based management or 'Inflammometry' is useful in eosinophilic asthma and results in improved outcomes,³⁸ in particular, a significant reduction in asthma exacerbations.³⁸⁻⁴¹ A severe asthma clinic allows clinicians to use inflammometry to guide therapy. Some patients with severe eosinophilic asthma,³ may respond to high dose systemic corticosteroids delivered via the intramuscular route, such as triamcinolone.³⁷ The exact mechanism for this is unknown but is likely to be multifactorial. It could be that parenteral steroids are able to reach more peripheral airways, or that they reach the bone marrow and may influence eosinophilopoiesis being upregulated by haemopoietic factors produced by inflamed tissue.^{37,42} Additionally, as intramuscular steroids are administered by clinic staff, this removes the risk of treatment non-adherence.

Omalizumab

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to free IgE and is effective as an add-on agent in severe persistent allergic asthma.^{5,43,44} It is administered as a subcutaneous injection either every 2 weeks or monthly depending on the dose required. The compound is generally well tolerated. There is a small risk of anaphylaxis (less than 0.1%).^{45,46} This is managed by administration in a suitable location, with assessable medical support, resuscitation drugs and equipment. Direct observation is recommended for 2 h after the first three omalizumab treatments, and 30 min thereafter.⁴⁵ Omalizumab is approved for use in Australia and provided by the PBS to approved patients (<http://www.medicareaustralia.gov.au>).

Itraconazole

Fungal sensitization is an important problem in severe asthma. It is detected by finding specific IgE directed at fungi, typically *Aspergillus fumigatus*. It can be extreme and manifest as allergic bronchopulmonary aspergillosis. In this condition, antifungal treatment with itraconazole is effective.^{47,48} However, the role of antifungal treatments in severe asthma remains to be defined.

Macrolides

Macrolide antibiotics are a well-characterized family of antimicrobials⁴⁹ that are now being investigated and used as immunomodulatory or anti-inflammatory agents in the treatment of chronic inflammatory airway diseases including severe asthma.⁵⁰ These

Table 6 Recommended trial period on and off treatment, outcome assessments and safety considerations

	LTRA	OCS	Macrolides	Itraconazole	Omalizumab	Tiotropium	Methotrexate/gold
Baseline assessment							
Treatment period	4 weeks	4 weeks	ACO, AQLQ, FEV ₁ , exacerbations, OCS use, sputum inflammatory cell counts, FeNO, IgE	16 weeks	16 weeks	4 weeks	16 weeks
Off-treatment period	4 weeks	Titrated dose reduction	12 weeks	4 weeks	4 weeks	2 weeks	?
Outcome assessment	ACO FEV ₁ Exacerbations OCS use	ACO FEV ₁ Exacerbations OCS use Sputum eosinophils or FeNO	ACO FEV ₁ Exacerbations OCS use Sputum neutrophils	ACO FEV ₁ Exacerbations OCS use	ACO AQLQ FEV ₁ Exacerbations OCS use	ACO FEV ₁ Exacerbations OCS use	ACO FEV ₁ Exacerbations OCS use
Safety assessments	Clinical evaluation	Clinical evaluation Bone mineral densitometry Cortisol, ACTH stimulation Diabetes monitoring based on screening assessment	Clinical evaluation Liver function test	Clinical evaluation Liver function test	Clinical evaluation FeNO	Clinical evaluation Screening for known contraindications	Clinical evaluation Liver function test Full blood count

ACO, asthma control questionnaire; ACTH, adrenocorticotropic hormone; AQLQ, asthma quality of life questionnaire; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

antibiotics have a broad spectrum of action which includes the regulation of leukocyte function and the production of inflammatory mediators, resolution of inflammation and control of mucus hypersecretion.⁵¹ Airway inflammation is heterogeneous in severe asthma.^{52,53} Macrolide antibiotics may improve quality of life and reduce exacerbations in neutrophil-mediated diseases such as cystic fibrosis, bronchiectasis, diffuse panbronchiolitis and asthma. A trial of macrolides in those patients with severe asthma and neutrophilic inflammation and/or mucus hypersecretion may be indicated.

Immunosuppressive therapy

Methotrexate, oral gold (auranofin) and cyclosporine have significant potential toxicity and limited efficacy which makes these agents of very limited usefulness. In Churg–Strauss syndrome, a form of systemic necrotizing vasculitis associated with severe asthma, and in eosinophilic pneumonia with severe asthma, immunosuppressive agents are used as oral steroid-sparing compounds.

Leukotriene receptor antagonists

Antileukotrienes or leukotriene receptor antagonists (LTRA) are included in asthma guidelines as add-on therapy for the treatment of severe asthma.¹⁹ The use of LTRA in a severe asthma clinic can be evaluated using modified $n = 1$ trials whereby the patient acts as their own control to determine treatment response.

Other long-acting bronchodilators

The place of other long-acting bronchodilators is less well established in severe asthma. One study found efficacy for theophylline.⁵⁴ Tiotropium may also have a role.⁵⁵

Speech pathology—treatment

Treatment for VCD involves a range of techniques to address the symptoms including education, teaching patients to identify early symptoms of impending VCD episodes, and to use a breathing technique such as Relaxed Throat Breathing or PVFM (paradoxical vocal fold movement) Release Breathing. Vocal hygiene education is an important aspect of therapy that also helps patients to identify triggers to symptoms and to manage exposure to these triggers. Counselling is also provided to help patients internalize responsibility for managing symptoms. Treatment for dysphonia associated with asthma or VCD involves a range of techniques including Stemple Vocal Function Exercises and components of the Lessac Maddison Resonant Voice Therapy techniques. Timely access to nasal endoscopy for biofeedback is unavailable but would be a useful adjunct to therapy.

Aspirin desensitization

Aspirin sensitivity can be a feature of severe asthma. Most cases can be controlled by conventional asthma therapy, but occasionally aspirin desensitization is used as an adjunctive management strategy.^{56,57}

Excessive β -agonist use

While β -agonists provide life-saving therapy for bronchospasm and effective short-term relief of wheeze, their use in excess can be problematic, leading to pro-inflammatory effects and increased airway hyper-responsiveness. Excess use of β_2 -agonists can be a feature of severe asthma, and potentially contribute to poor asthma control.⁵⁸ This problem requires a structured and multidisciplinary approach, as offered in a severe asthma service. With cooperative involvement of the affected patient, β -agonist therapy is minimized or even withdrawn and asthma control is regained.

EVALUATION

Data management, quality assurance and opportunities for research

In an earlier review of this series, Hooper *et al.* acknowledge that the management of patients within a specialist service provides an opportunity to establish prospectively maintained clinical databases.⁵⁹ The benefits of a well-established system which facilitates systematic data collection are multiple. It can improve individual patient management as the system will allow review of previous treatment trials and responses and provide details of ongoing asthma control and skills. Such a system will enable evaluation of a severe asthma service and provide a means to review the service for continuous quality improvement purposes, and will facilitate both clinical audits and research. There is a need for high quality clinical research in severe asthma² and a severe asthma service is an opportune environment to conduct research trials in a clinical setting.

BARRIERS OR HURDLES IN SETTING UP A SEVERE ASTHMA SERVICE

Perhaps the most obvious hurdle in setting up a severe asthma service is identifying and obtaining the requisite resources. These involve clinician time as well as access to expensive drugs to effectively manage severe asthma. Our approach in the initial set-up of this service was to apply a 'cost-shifting' approach. A pre-existing asthma clinic staffed by a respiratory physician and clinical nurse consultant was redeveloped as a severe asthma service, limiting the cost implications. Similarly the speech pathologist relocated an existing speech pathology clinic located in the Allied Health department and allocated the staffing to the severe asthma service within the

Respiratory Department. Creating change to current practice as opposed to starting from scratch will reduce the cost burden of such a service.

Access to expensive drugs is another challenge faced in a service asthma service. Providing access to treatment through the severe asthma service will improve patient adherence to therapy and hence patient outcomes. The challenge is that this becomes a cost to the health-care service. A business case should be developed involving an application to the hospital drug committee to fund effective treatments that are not available through the PBS. Whilst this is an added expense, in our service it has become a cost effective solution by minimizing acute health-care utilization, and leading to cost minimization by limiting access to expensive drugs to proven responders.

Initially referral by other specialist physicians may be slow. Good communication with the referral sources has allowed us to overcome any potential problems. Initially we provided a written introduction about the service to all potential referrers; this included a description of the service's aims and objectives, the processes, the treatments available and importantly the process for patients exiting the service and returning the patient to usual care after the assessment was complete. Moreover, we presented the service development and evaluation at departmental meetings of the junior and senior medical officers. Written feedback is provided by the severe asthma team detailing progress and treatment responses. These measures have allowed us to effectively engage the physicians as active referrers to the service.

Poor uptake by patients is another hurdle that must be considered. Patient adherence in severe asthma is often poor despite persistent symptoms; one reason for poor adherence relates to the financial expense to the patient.²³ As treatment is escalated, the cost of therapy is also increased. Provision to patients of access to treatment that they may not feasibly be able to afford can improve adherence to treatment. A contract should be developed with the patient and the severe asthma team in terms of their regular attendance at the clinic and their use of medications as prescribed. Patients with severe asthma also have frequent absenteeism from employment, school or tertiary studies due to acute exacerbations. The additional time required to attend clinics may add to their absenteeism and therefore increase the non-attendance rate to the service. Improvements in clinic attendance can be achieved by holding the clinics in the afternoon up until 5–6 PM in order to minimize further absenteeism in the patients' place of work or study.

FUTURE DIRECTIONS

A severe asthma service must be continually evolving. As new therapies become available there must be mechanisms to introduce these treatments in the clinics. This is likely to increase the staffing requirement and the cost of treatment. To improve the funding of such services we must gather large

datasets to demonstrate the effectiveness of multidimensional service provision. The development of a national severe asthma network may be an effective approach to allow generation of these data and to further inform service provision.

CONCLUSIONS

Severe asthma places a significant burden on the health-care system and negatively impacts patients' health status. A severe asthma service provides a multidisciplinary approach to the management of severe asthma which enables confirmation of diagnosis and optimization of asthma management and self-management skills. Importantly, a severe asthma service enables an environment to address the aggravating and comorbid conditions that complicate management and provides an environment which can safely and effectively evaluate add-on pharmacotherapies. In addition to improving patient outcomes, a severe asthma service provides important training and research opportunities. We have described the central components needed to set up such a service.

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