

CASE-BASED LEARNING

'SIMPLES': a structured primary care approach to adults with difficult asthma

*Dermot Ryan¹, Anna Murphy², Bjorn Stallberg³, Noel Baxter⁴, Liam G Heaney⁵

¹ General Practitioner, Woodbrook Medical Centre, Loughborough, UK; Honorary Clinical Research Fellow, Allergy and Respiratory Research Group, The University of Edinburgh, Edinburgh, UK

² Consultant Respiratory Pharmacist, University Hospitals of Leicester NHS Trust, Department of Respiratory Medicine, Glenfield Hospital, Leicester, UK

³ General Practitioner, Department of Public Health and Caring Science, Family Medicine and Preventive Medicine, Uppsala University, Sweden

⁴ General Practitioner, Surrey Docks Health Centre, Downtown Road, Surrey Quays, London, UK

⁵ Professor of Respiratory Medicine, Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, N Ireland

Commissioned article; externally peer-reviewed; received 30th June 2013; accepted 31st July 2013; online 23rd August 2013

Summary

The substantial majority of patients with asthma can expect minimal breakthrough symptoms on standard doses of inhaled corticosteroids with or without additional add-on therapies. SIMPLES is a structured primary care approach to the review of a person with uncontrolled asthma which encompasses patient education monitoring, lifestyle and pharmacological management and addressing support needs which will achieve control in most patients. The small group of patients presenting with persistent asthma symptoms despite being prescribed high levels of treatment are often referred to as having 'difficult asthma'. Some will have difficult, 'therapy resistant' asthma, some will have psychosocial problems which make it difficult for them to achieve asthma control and some may prove to have an alternative diagnosis driving their symptoms. A few patients will benefit from referral to a 'difficult asthma' clinic. The SIMPLES approach, aligned with close co-operation between primary and specialist care, can identify this patient group, avoid inappropriate escalation of treatment, and streamline clinical assessment and management.

© 2013 Primary Care Respiratory Society UK. All rights reserved.

D Ryan *et al.* *Prim Care Respir J* 2013; 22(3): 365-373

<http://dx.doi.org/10.4104/pcrj.2013.00075>

Keywords difficult asthma, primary care, asthma control

Introduction: the problem of poor asthma control

Asthma has a high prevalence throughout Europe and the industrialised nations, with increasing prevalence in developing economies probably as a consequence of life style changes.^{1,2} For a variety of (often correctable) reasons many people with asthma do not gain full control of their condition,³ and there are marked variations in outcomes of care between hospitals and between primary care practices.^{4,5} The only example of a systematic national approach to the management of asthma (in Finland) demonstrated significant patient benefit coupled with large cost savings.⁶ This programme was based on education of healthcare professionals and promotion of self-management, with the aim of achieving accurate diagnosis and high quality structured management.

The SIMPLES approach to poorly controlled asthma

SIMPLES is a structured approach to the review of a person with uncontrolled asthma which encompasses self-management education monitoring, lifestyle and pharmacological management and addressing support needs. See Table 1 for a summary of the components of SIMPLES.

After a succession of structured reviews over a short time frame, most patients' asthma will have been brought under control. Those who have not achieved control by this process are identified as needing referral to specialist care for further evaluation. Some of these patients will have severe or atypical 'therapy resistant' asthma (see the first case study), some will have psychosocial problems which make it difficult for them to achieve asthma control (see the

* Corresponding author: Dr Dermot Ryan, Woodbrook Medical Centre, 28 Bridge St, Loughborough, LE11 1NH, UK.

Tel: +44 (0)7950 200333 Fax: +44 (0)1509 239649 E-mail: dermotryan@doctors.org.uk

Table 1. The SIMPLES approach to the primary care management of 'difficult to manage' asthma

For general advice and resources linked to all the SIMPLES points:

<http://www.theipcr.org/display/DIFFMANAST/Home+-+Difficult+to+manage+asthma>

	Acronym	Explanation	Resources
S	Smoking status	Smoking has an adverse effect on asthma control, possibly by causing a relative resistance to inhaled corticosteroids. ⁷⁰ Every effort should be made to identify smokers and to assist in smoking cessation.	IPCRG: Tackling the smoking epidemic. http://www.theipcr.org/display/RESSMO/Tackling+the+smoking+epidemic NCSCT: Very Brief Advice training module," 2012. http://www.ncsct.co.uk/publication_very-brief-advice.php . NICE PH10: Smoking cessation services http://publications.nice.org.uk/smoking-cessation-services-ph10
I	Inhaler technique	Poor control is commonly due to poor inhaler technique, ^{71,72} and it is the responsibility of every health care professional who prescribes an inhaler device to ensure that the patient knows how to use that device. ⁷³ Asthma control may be improved by the simple expedient of correcting inhaler technique, adding a spacer device or changing the inhaler to one which is more easily used. Unfortunately, many health care professionals are unable to use inhalers, ⁷⁴⁻⁷⁶ so that they are ill-equipped to either assess or teach inhaler technique. The difference in technique between dry powder and metered dose inhalers is considerable and confusing, ⁷⁷ so it is prudent, where possible, to administer inhaled medication to a patient using only one kind of device.	Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. <i>Prim Care Respir J</i> 2009; 18 :243-9 http://www.thepcrj.org/journ/view_article.php?article_id=633
M	Monitoring	Cochrane reviews recommends that patients self-monitor using symptoms and/or lung function measurements. ^{8,78} Standard morbidity questions (e.g., the RCP three questions) would seem ideal for self-interrogation on a daily basis: Did my asthma wake me last night? Am I having any of my usual asthma symptoms? Is my asthma stopping me from doing anything? If the answer is 'no' to all three then they should carry on with their usual regime. If the answer is, yes, it should prompt self-enquiry: Did I take my inhaler? Is there medication in my inhaler? Has anything else happened (e.g., allergen exposure, viral infection) Is this to do with my new occupation/hobby? Those who have difficulty in perceiving symptoms, should monitor peak flow readings to guide increase or decrease in treatment.	IPCRG user's guide to asthma control tools https://www.theipcr.org/download/attachments/688342/asthma_control_tools.doc?version=1&modificationDate=1334845550000 Asthma Control Test (ACT) http://www.asthma.com/resources/asthma-control-test.html Asthma Control Questionnaire (ACQ) http://www.qoltech.co.uk/acq.html
P	Pharmacotherapy	Most people with asthma will need daily treatment with ICS (step 2) to control their asthma often at relatively low doses, ^{13,14} which avoids any risk of adverse effects, such as osteoporosis, adrenal suppression and diabetes. ^{79,80} Addition of LABAs to ICS (step 3) improves outcomes such as lung function and symptoms and decreases asthma-related hospitalisations and mortality. ⁸¹ SABA relieve asthma symptoms and monitoring of SABA use is helpful in assessing asthma control: good asthma control is associated with little or no need for SABAs. ^{13,14} Adherence to preventer medication is often poor and should be checked at every review. Prescription refills are a practical way of assessing adherence	Global Initiative for Asthma http://www.ginasthma.org/ British Thoracic Society/Scottish Intercollegiate Guideline Network. http://www.sign.ac.uk/
L	Lifestyle	Attention to general lifestyle advice on diet, exercise, alcohol, weight maintenance and smoking cessation can improve outcomes: in particular exercise should be encouraged. In addition advice on avoidance of known triggers is useful along with advice to have an annual influenza vaccination. It is important to enquire into comorbidities such as eczema, gastro oesophageal reflux disease, rhinitis, social and psychological factors. People affected by pollen should have specific advice about co-treatment of rhinitis and when to start this.	Allergic Rhinitis and its Impact on Asthma http://www.whiar.org/
E	Education	Structured education should include: <ul style="list-style-type: none"> • Understanding the condition • Understanding the medications, when and how to take them • Inhaler technique • Self-monitoring (symptoms, peak flow) with instructions on what to do when there is a decrease in control (reinforced by a written action plan) • What to do in an emergency, or what to do when my action plan does not appear to be working. 	Various national charities have relevant and useful information posted on their websites such as AsthmaUK at http://www.asthma.org.uk/knowledge-bank . A list of many European Asthma Charities may be found at http://www.efanet.org/efa-members/
S	Support	Healthcare professionals lend support by performing structured reviews at a frequency appropriate to the patients' needs. Ease of access in times of crisis is also important, to ensure that exacerbations are identified and treated early. Many countries have patient support charities which can provide support in a variety of ways. On diagnosis patients could be directed to their national organisations websites and take from them those aids which they find helpful. Support may also be given by family groups or patient support groups at a local level.	European Lung Foundation has useful information in several languages. http://www.european-lung-foundation.org/

SIMPLE[®]Anna Murphy, 2012

(adapted from <http://www.tin.nhs.uk/innovation-nhs-east-midlands/innovation-in-practice/regional-innovation-fund-projects-2009-10/simple-approach-to-asthma-management/>)

second case study) and some may prove to have an alternative diagnosis driving their symptoms.⁷ If the diagnosis is in doubt, spirometry performed while the patient is symptomatic should confirm reversible obstruction. Referral for a bronchial challenge test or assessment of airway inflammation may be needed.

Regular review and self-monitoring

Ideally monitoring should be undertaken both by a healthcare professional during regular planned and structured reviews, and by daily self-monitoring (of symptoms and/or peak expiratory flow, as preferred) by the patient. These overlap, of course, as self-monitoring should always be supported by the healthcare team during structured reviews at a frequency appropriate to the patient's needs.⁸ Ease of access in times of crisis is also important, to ensure that exacerbations are identified and treated early.

In order to self-monitor effectively the patient needs to have an accurate understanding of their condition after receiving education about various aspects of asthma and its management. The literature on self-management education stretches back over some thirty years. The single most consistent finding is that patients who receive structured education and have a written personalised plan have a significant reduction in exacerbations or hospital admissions.⁸

The advent of telehealth and internet-based applications may help improve outcomes by enabling real-time support for self-monitoring.⁹ A recent study of self-monitoring using traditional paper charts or recording data on a mobile phone and receiving instantaneous feedback did not demonstrate a difference in control between the groups, though patients in both groups demonstrated a clinically meaningful improvement in asthma control.¹⁰ Comprehensive internet-based guided self-management improved asthma control, with more patients achieving a clinically significant improvement than in the usual care group.¹¹ Recently, the utility of mobile phone technology to identify exacerbations of asthma has been demonstrated.¹² Improving technology may produce a digital solution which can be used to support patients with 'difficult to control' asthma in gaining and maintaining control.

Pharmacotherapy

Asthma guidelines recommend a stepwise approach to the treatment of asthma.^{13,14} The aim is to achieve and maintain control by stepping up treatment as necessary and stepping down when control is good. A decision to increase treatment should not be made until it has been confirmed that a person can demonstrate optimal inhaler technique, has access to and is taking their treatment as recommended, and is taking adequate measures to avoid allergens and triggers.¹⁵ Correcting these factors can often improve asthma control and prevent unnecessary escalation of treatment.¹⁶⁻¹⁹

Non-adherence to inhaled corticosteroids (ICS) is a common cause of poor asthma control.²⁰ For many reasons (including lack of understanding of the roles of different forms of therapy, fear of steroids, financial concerns) only 30-70% of patients take preventative therapy as instructed.²¹ Many patients forget to take one or more doses each day or stop taking their preventative inhaler

when they feel better, only to have a recurrence of asthma symptoms a few weeks later. Identification of non-adherence is fundamental to managing apparently refractory disease. Medication adherence can be improved by providing information on treatment, allaying fears, and negotiating with the patient as to how they can take their therapy taking into account their individual lifestyle.^{18,19}

Resources

As part of an initiative on 'difficult to manage asthma',²² the International Primary Care Respiratory Group (IPCRG) has produced a desktop helper with the SIMPLES checklist and a number of other tools to support primary health care professionals in their daily practice. This and other useful resources are given in Table 1.

Case study 1. A woman with difficult to manage asthma

A 40 year old non-smoking woman, working as a teacher, with a history of asthma since she was 25 years old, attends the clinic to request another prescription. Despite taking a moderate/high dose combination inhaler (inhaled steroid + long-acting β_2 -agonist) which she is requesting regularly, she uses two reliever inhalers a month. She had two exacerbations in the previous year which responded well to oral corticosteroids. Over the years she has tried a leukotriene receptor antagonist, oral long-acting β_2 -agonist, and theophylline, none of which produced any lasting benefit. Four years ago, spirometry showed moderate obstruction with good reversibility though the post-bronchodilator forced expiratory volume in one second (FEV₁) did not return to normal.

Difficult to manage asthma in adults is a challenge.²³ Even if this case history is not the most common among asthma patients in primary care practice it is still not unusual. The review of a patient with difficult to manage asthma includes evaluation of several factors: the SIMPLES approach provides a helpful checklist.

Medical history: co-existing conditions

It is important to review the clinical history. The patient is a non-smoker. Does she have any other co-existing conditions or comorbidities which may have an impact on her asthma control?

- Non-steroidal anti-inflammatory drugs and aspirin intolerance are recognised causes of severe asthma and often overlooked. In clinical practice it is not unusual that asthma patients have been prescribed an oral β -blocker for hypertension or ischaemic heart disease, or topical β -blockers for glaucoma which may worsen their asthma.
- Cough may be an indicator of gastro-oesophageal reflux, but the relationship between reflux and poorly controlled asthma is not clear.²⁴ Treatment with proton-pump inhibitors does not improve asthma control in patients with asymptomatic reflux.²⁵
- It is also important to consider allergic and non-allergic triggers which may worsen her asthma. Asthma and rhinitis frequently coexist and if this patient has symptoms of rhinitis it will be

important to treat the rhinitis according to guidelines.²⁶ This is important, as both rhinitis and asthma symptoms could be aggravated by allergies. Allergy testing may help confirm or refute a suspected allergic cause for her poor control.

- Another cause which needs to be considered is occupational asthma,²⁷ though this is unlikely in this lady who is a teacher.
- Looking for dysfunctional breathing and other conditions such as vocal cord dysfunction and bronchiectasis is also important as they may contribute to asthma-like symptoms.^{28,29}

Monitoring asthma control

Assessing the patient's asthma control is important. There are several tools which are easy to use – for example, the RCP 3 Questions³⁰ – which have been tested in clinical practice.³¹ Other common validated questionnaires are the Asthma Control Test (ACT) with five questions assessing symptoms over the last four weeks,³² the Asthma Control Questionnaire (ACQ) with seven questions about symptoms in the last week,³³ and CARAT, a 10-question test assessing the control of both allergic rhinitis and asthma in the last four weeks.³⁴ In their clinical review in this issue of the *PCRJ*, Blakey *et al.* discuss the importance of not only assessing asthma control but also the future risk of asthma attacks.³⁵

In this case, the patient's history of frequent exacerbations and frequent use of relievers not only indicate uncontrolled asthma but also a significant future risk of further exacerbations despite a high treatment level. Self-management education supported by a personalised asthma action plan and an emergency supply of oral steroids is an important aspect of this lady's care.^{8,13,14}

In patients with difficult to manage asthma and persistent exertional breathlessness such as this lady it is important to look for fixed airflow obstruction (usually related to airway remodelling or smoking) which may not be responsive to treatment escalation.³⁶ In this case, the post-bronchodilator FEV₁ four years ago could not be reversed to normal suggesting that this might be a problem. Up-to-date spirometry would be helpful to assess any deterioration in fixed airflow obstruction.

Inhaler technique

This patient has uncontrolled asthma despite 'step 3' treatment,^{13,14} and she assures her doctor that she uses her inhalers regularly (although this should be confirmed by assessing the refill prescribing record, as patient report may be unreliable). There is evidence that many patients are unable to use their inhalers correctly, regardless of the device. Poor inhaler technique is associated with poor asthma control.^{37,38}

Guidelines recommend that inhaler technique should be checked in all patients, particularly those with uncontrolled asthma,^{13,14} and this is highlighted in the SIMPLER tool. Inhaler technique training is a cornerstone in the management of all patients with asthma in order to ensure optimal therapy,³⁹ with a range of different possibilities in the choice of inhaler.⁴⁰

Pharmacotherapy

Before evaluating whether the patient is treated at the right step to achieve control, the SIMPLER approach recommends discussing both adherence and understanding of the treatment. The teacher in this case had no specific reasons for her poor control so a step-up in

treatment should be considered. There are several treatment options at step 4: increasing ICS up to a daily dose of 1,000 µg fluticasone (FP) or equivalent, adding a leukotriene receptor antagonist (LTRA), or treatment with a theophylline.^{13,14} If a trial of additional treatment is ineffective it is important to stop the add-on treatment or reduce the dose of ICS to previous levels to minimise the risk of systemic side effects. Considering the safety profile of ICS is important. Doses up to 400 µg daily FP or equivalent are regarded as having minimal long-term side effects, whereas patients treated with higher doses of ICS for a longer period or with repeated courses of oral corticosteroids have an increased risk of steroid-related adverse effects.^{13,14}

There is increasing evidence that abnormalities in the small airways may contribute to severity of disease. A recent systematic review showed that small-airways dysfunction was associated with worse asthma control and suggested that treatment with extra-fine particle ICS could improve symptoms and asthma control in those patients with small-airways disease.⁴¹ This may be another option for treatment in this lady.

Case study 2. A man who has difficulty managing his asthma

A 32 year-old man attends for an unscheduled appointment asking for a course of oral corticosteroids and another sick note as his asthma is worse than usual. From his history it is clear that he has had troublesome asthma since childhood. His regular prescription is for a high dose inhaled steroid/long-acting β₂-agonist combination inhaler, as well as montelukast, theophylline and a nasal steroid spray. He has also taken citalopram intermittently over the last few years. The prescribing record shows that he has had eight courses of oral corticosteroids in the last year, and he has had three hospital admissions in the last few years. His last routine review at the asthma clinic was six years ago, when it was noted that he was trying to quit smoking.

This man attends frequently for healthcare but when he does he is in crisis and it is often too late for primary care management alone. These emergency visits will inevitably focus on acute management but attempts should also be made to engage him in a follow-up visit in order to work through the reasons for his loss of control. Creating an opportunity for a holistic review should be a key aim, since planned care with a GP when asthma is stable can improve asthma control.⁴² UK standards now recommend booking a review by a GP within 48 hours of an unplanned asthma event.⁴³ A key component of the review will be the provision of a personalised action plan.

In the presence of such complexity the use of the SIMPLER algorithm can support a comprehensive overview that can be followed up with focused appointments about the identified adherence and precipitating factors.

Smoking cessation

Smoking worsens asthma symptoms, increases exacerbations and hospitalisations and is associated with an increased risk of

mortality.^{44,45} This man has received or is currently receiving pharmacotherapy for conditions known to worsen asthma such as nasal allergy and depression or anxiety, but there is no evidence that he has received smoking cessation medication and this may be a potential blind spot when considering treatment of exacerbating factors. The last recorded smoking status in this patient was six years previously with no record of an intervention to support his quit attempt. This could have been a result of his failure to attend planned care but could also be due to the health professionals' attitudes or beliefs about the effectiveness of smoking cessation in highly addicted smokers who persist despite the effect on their illness.⁴⁶

Stopping smoking can both decrease the risk of future disease and help improve his current control.⁴⁷ This man is at risk of fixed airways disease (COPD) because of the combination of poor control and smoking.⁴⁸ In this (and at every appropriate) general practice consultation we need to provide brief advice using behavioural change techniques. This involves assessing current and past smoking, possibly monitoring carbon monoxide levels, advising on effects of continued smoking, explaining briefly how stop smoking treatments work and then initiating appropriate pharmacotherapy and arranging future support. Patients expect and are happy to be asked this in a healthcare setting.⁴⁹

One of the benefits of stopping smoking – and an important factor to communicate to this man – is that lower doses of ICS may then be effective. Tobacco smoke inhibits the effect of steroids on airway inflammation so that smokers require escalating doses of ICS, putting them at risk of systemic steroid effects. His combined steroid use from nasal, inhaled and oral routes currently exceeds 1000 µg FP equivalent per day and he should therefore be provided with a steroid card. Whilst working with this man to help him quit smoking there is some evidence that other medicines such as LTRAs, inhaled anticholinergics and LABAs may improve asthma outcomes in smokers.⁵⁰⁻⁵³

Lifestyle factors

The SIMPLES checklist reminds us to explore lifestyle factors and for this man there is some evidence that his work may be important. He asks for a sick note at the same time as a crisis. A number of factors may play a part, such as work stress that may be exacerbating anxiety or depression, or he may have specific occupational exposure from which he needs to be removed. Removal from, or reduced exposure to, an occupational trigger should improve control (especially if it is initiated soon after the onset of sensitisation). It is important to balance the clinical benefit against the social or psychological harms that may arise from the risk of unemployment that follows a diagnosis of occupational asthma.⁵⁴

Psychosocial problems

Depression is associated with difficult asthma and the record of citalopram prescribing suggests he has been treated for this condition. Support for this man therefore needs to be considered from a number of perspectives such as depression, work and smoking. We know that low levels of health-related quality of life in asthma are associated with current or past smoking history, severity of symptoms and absence from work.⁵⁵ As a clinician it is possible to support him not just through direct medical care but also through

signposting to support that may be available locally. This might include a counselling service, a health trainer, online and telephone support from organisations such as patient charities. However, patients may also have personal resources locally that they have not considered using. How can family, friends, neighbours or even work colleagues be utilised to support him? Has he told them what is happening and could you help him consider resources close to home?

Referral to the 'difficult asthma' clinic

When should a referral be made?

The substantial majority of patients with asthma can expect minimal breakthrough symptoms on standard doses of ICS therapy with or without additional add-on therapies. In the primary care setting, a 'red flag' strategy of proactively identifying and systematically reviewing patients who are prescribed treatment at Step 4 or 5,^{13,14} particularly those who fail to achieve symptom control or have recurrent 'exacerbations', should be applied. This will prevent inappropriate escalation of treatment and identify patients who should be assessed in more detail, both within the primary care setting or with referral to a difficult asthma service.

The small group of patients presenting with persistent asthma symptoms despite being prescribed high levels of treatment are often referred to as having 'difficult asthma'. A pragmatic definition of difficult asthma is persistent respiratory symptoms despite treatment with a LABA and high dose ICS (≥ 1000 µg FP equivalent) which equates to people who remain symptomatic at step 4 or requiring treatment at step 5 of guidelines.^{13,14} It is important to differentiate the term 'difficult asthma' from 'therapy-resistant asthma' or 'severe refractory asthma'; these latter terms encompass patients who are relatively treatment resistant and generally require high doses of steroid therapy or additional biological treatments to achieve control, whereas patients with 'difficult asthma' often have more therapy-responsive disease but may have different factors which cause them to have persistent symptoms.^{23,56,57}

What can a 'difficult asthma' clinic offer?

The initial phase of assessment in a 'difficult asthma' clinic involves addressing the fundamental issues using a systematic approach, and a series of key questions about accuracy of diagnosis, medication adherence and inhaler technique, and potentially modifiable aggravating factors which should be considered before committing patients to further high dose treatment (see Table 2).

In the 'difficult asthma' clinic, these issues are systematically identified and managed by the multi-disciplinary team;^{23,56,57} this can include trials of therapy along with more detailed investigation such as detailed lung function, high resolution CT scanning, measures of airway inflammation (e.g. induced sputum, exhaled nitric oxide), psychological assessment and management with either medication or clinical psychology input, echocardiography, cardiopulmonary exercise testing, plus other investigations as required. Clinical assessment with spirometry during an episode of worsening symptoms can help to distinguish patients with worsening asthma from other conditions causing increased breathlessness, as this can sometimes be the reason for acute events unresponsive to asthma treatment.

Table 2. Potentially modifiable aggravating factors which should be considered before escalating treatment

Does the patient have asthma?

Are all of their symptoms due to asthma?

Are they taking their treatment as prescribed and appropriately?

Are there additional potentially modifiable aggravating factors?

- psychological factors
- dysfunctional breathing
- upper airways disease
- bronchiectasis
- gastro-oesophageal reflux
- obesity
- occupational factors
- inhaled allergen exposure
- medication e.g. β -blockers, aspirin, non-steroidal anti-inflammatory drugs
- obstructive sleep apnoea
- systemic disease (thyrotoxicosis, Churg-Strauss syndrome, carcinoid syndrome)

Note - this list is not all-inclusive but lists some of the commoner issues identified

Specific conditions

Specific problems such as vocal cord dysfunction, dysfunctional breathing, and bronchiectasis will be managed with appropriate multi-disciplinary input, along with optimisation of asthma therapy (if appropriate) to try and achieve symptom control.

After thorough evaluation and management, some patients will have 'refractory asthma', which is defined as persisting asthma symptoms despite adherence with high dose treatment. These patients often have a propensity to asthma exacerbations, with frequent use of courses of oral corticosteroids despite prescription of add-on therapies e.g. LTRAs or theophylline, and may require maintenance oral corticosteroids.^{58,59} In general, following systematic evaluation and a detailed assessment, between one-third and a half of patients with 'difficult asthma' will have therapy resistant disease, with other diagnoses, co-morbidities, non-adherence or psychosocial factors explaining symptoms in the others.^{19,56}

Therapeutic options

There are a number of therapeutic options available in refractory asthma. For some patients, low dose maintenance oral corticosteroid therapy is well tolerated and effective, but for many, systemic steroid therapy either causes significant side-effects or does not produce disease control, and some patients display steroid insensitivity.

Current therapeutic options for such patients include:

- Immunomodulatory corticosteroid-sparing drugs such as methotrexate, cyclosporin and gold. These agents have marked variability in efficacy, may result in significant adverse effects and

benefits do not persist after stopping treatment.¹⁴ Guidelines recommend that these medications should be reserved for patients who have not responded to usual treatments, and that risks and benefits should be closely monitored.^{13,14}

- Omalizumab. This humanised monoclonal antibody reduces free IgE by almost 95% by blocking the binding of IgE to its specific high-affinity receptor.⁶⁰ Over 50% of patients with refractory asthma have allergic IgE-mediated disease,⁵⁹ and omalizumab is a therapeutic option for those patients with serum IgE levels in the range 30 to 1500 IU/ml. Anti-IgE therapy is recommended by guidelines for patients at step 5^{13,14} and is administered by subcutaneous injection at 2- or 4-weekly intervals. Due to the high cost of this treatment, different countries have specific criteria to maximise benefit in selected populations of patients. Treatment should be initiated only after specialist assessment, should be monitored closely, and discontinued if it is not beneficial.
- Inhaled long acting anti-muscarinic agents (LAMAs). Recent data with tiotropium shows some additional benefit in patients already prescribed LABA/ICS with persistent symptoms and airflow obstruction.⁶¹ In the next few years other ultra-long-acting LAMA and LABA preparations will become available and will require evaluation in severe asthma.
- Bronchial thermoplasty is a technique that involves the delivery of radio frequency energy to the airways during bronchoscopy with the aim of reducing airway smooth muscle mass and responsiveness in asthma.⁶² Several studies have demonstrated efficacy and safety for this treatment in selected patients,⁶³ but the degree and duration of benefit, and which patients with severe asthma will benefit most, remain to be clearly established.
- Novel biological agents which will target 'Th2 inflammation' (elevated interleukin-4, interleukin-5 and interleukin-13) and are likely to be available in the next 2 – 3 years.⁶⁴⁻⁶⁶ Although there is likely to be some overlap with the population suitable for omalizumab, these new therapies are not specifically targeted at allergic disease. A 'stratified' approach to severe asthma, which focusses on targeting complex therapies at patients with the appropriate inflammatory phenotype is likely to be a core component of work in the severe asthma clinic in the future.⁶⁷
- Anti-fungal therapy may have a role in patients with chronic allergic bronchopulmonary aspergillosis (ABPA) and other fungally-sensitised severe asthma patients.^{68,69}

How can the primary care physician help support care? – the ideal referral letter...

As with many conditions, the assessment and control of patients with difficult asthma can be optimised with a close cohesive partnership between primary and secondary care. Many of the initial questions around diagnosis, adherence and co-morbidity can be addressed in primary care and this detail can be covered in the referral letter. This will provide much of the information required in the initial assessment in the difficult asthma clinic. By way of example, a referral letter with much of the relevant detail is presented in Figure 1.

Figure 1. An exemplar referral letter

Dear Doctor

I would value your assessment of this 42 year-old woman with asthma, who has never smoked tobacco.

She was diagnosed with asthma aged 7 years with clearly documented excellent response to inhaled steroid therapy at that time and has been on inhaled steroids more or less continuously since then, with minimal symptoms, no exacerbations requiring oral steroids and has never been admitted to hospital.

However in the past 18 months, she has become more difficult to manage and has had 2 hospital admissions and at least 6 additional visits to Accident and Emergency and our practice with worsening asthma. She receives oral steroids on each of these occasions and I have been concerned about her level of steroid exposure. Because of this, I reviewed these episodes and they do sound like asthma exacerbations with appropriate physical signs and reduced peak flow. On at least one of these presentations, she performed spirometry in the practice and this demonstrated airflow obstruction.

She is currently being prescribed a flixotide/salmeterol 500 Accuhaler 1 puff bd, montelukast 10 mg nocte but continues to require a salbutamol inhaler weekly. Her flixotide/salmeterol and montelukast prescription records are consistent with good prescription filling and her inhaler technique seems excellent.

She has no obvious co-morbidities other than some background rhinitis, which we have treated effectively with a nasal steroid and her BMI is 26. There has been no obvious change in her circumstances in the past few years and the home situation seems fairly stable. She is a housewife.

She had a normal chest x-ray 6 months ago and I have requested a bone scan because of her significant steroid exposure.

Many thanks

Conclusion

'Difficult to manage' asthma is not in itself a diagnosis but is a clinical problem which is clearly defined and which requires detailed assessment as outlined above. The SIMPLES approach, aligned with close co-operation between primary and specialist care, can identify this patient group, avoid inappropriate escalation of treatment, and streamline clinical assessment and management. Some patients will have severe refractory asthma. Novel therapies, many with companion disease biomarkers to allow targeting of these therapies to the correct patient, will be available in the difficult asthma clinic in the coming years.

Handling editor Hilary Pinnock

Acknowledgement The authors gratefully acknowledge their debt to Hilary Pinnock, the Handling editor, whose encouragement, input and editing was invaluable.

Conflicts of interest DR has no conflicts of interest to declare in relation to this article.

AM has had speaker fees (Almirall, AstraZeneca, Chiesi, GSK, Pfizer, Teva), Advisory Boards (Almirall, Boehringer, Chiesi Ltd, Napp, Novartis) and research funds (Almirall, GSK, Napp)

BS has received honorariums for educational activities and lectures from AstraZeneca, GlaxoSmithKline, Meda, MSD, Nycomed and has served on an advisory board arranged by AstraZeneca, Novartis and Boehringer Ingelheim.

NB has no conflicts of interest to declare

LGH has received grant funding from Medimmune, Novartis UK, Genentech Inc, and GlaxoSmithKline, has taken part in Advisory Boards and given lectures at

meetings supported by GlaxoSmithKline, Merck Sharpe & Dohme, Nycomed, Boehringer Ingelheim, Napp, Chiesi, Novartis and AstraZeneca. He has received support funding to attend International Respiratory meetings (AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim, Napp and GlaxoSmithKline) and has taken part in asthma clinical trials (GSK, Roche and Genentech) for which his Institution was remunerated. None of these activities have any direct relationship to the content of this manuscript.

Contributorship DR and AM wrote the overview of the SIMPLES approach, BS and NB wrote case studies 1 and 2 respectively, and LH wrote the section on the difficult asthma clinic. The handling editor (HP) collated and edited the individual sections.

Funding This work received no funding.

References

- Masoli M, Fabian D, Holt S, *et al*. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;**59**:469-78. <http://dx.doi.org/10.1111/j.1398-9995.2004.00526.x>
- Valovirta E for European Federation of Allergy and Airways Diseases Patients' Associations, EFA Book on Respiratory Allergies. Available from <http://www.efanet.org> (accessed July 2013)
- Rabe K F, Adachi M, Lai C K W, *et al*. Worldwide severity and control of asthma in children and adults: the global Asthma Insight and Reality surveys. *J Allergy Clin Immunol* 2004;**114**:40-47. <http://dx.doi.org/10.1016/j.jaci.2004.04.042>
- Price D, Horne R, Ryan D, Freeman D, Lee A. Large variations in asthma control between UK general practices participating in the asthma control, concordance and tolerance (ACCT) Initiative. *Prim Care Respir J* 2006;**15**:206 (AB574)
- Department of Health. Interactive Health Atlas for Lung conditions in England (INHALE) Available from <http://www.inhale.nhs.uk> (accessed July 2013)
- Hahtela T, Tuomisto LE, Pietinalho A, *et al*. A 10 year asthma programme in Finland: major change for the better. *Thorax* 2006;**61**:663-70. <http://dx.doi.org/10.1136/thx.2005.055699>
- Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. *Lancet* 2005;**365**:974-976. [http://dx.doi.org/10.1016/S0140-6736\(05\)71087-4](http://dx.doi.org/10.1016/S0140-6736(05)71087-4)
- Gibson PG, Powell H, Wilson A, *et al*. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No.: CD001117. <http://dx.doi.org/10.1002/14651858.CD001117>
- Pinnock H, Slack R, Pagliari C, Price D, Sheikh A. Understanding the potential role of mobile phone based monitoring on asthma self-management: qualitative study. *Clin Exp Allergy* 2007;**3**:794-802. <http://dx.doi.org/10.1111/j.1365-2222.2007.02708.x>
- Ryan D, Price D, Musgrave SD, *et al*. Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. *BMJ* 2012;**344**:e1756
- van der Meer V, Bakker M, van den Hout WB, *et al* for the SMASHING Study Group. Internet-Based Self-management Plus Education Compared With Usual Care in Asthma: A Randomized Trial. *Ann Intern Med* 2009;**151**:110-20. <http://dx.doi.org/10.7326/0003-4819-151-2-200907210-00008>
- Kupczyk M, Haque S, Sterk PJ, *et al*. Detection of exacerbations in asthma based on electronic diary data: results from the 1-year prospective BIOAIR study. *Thorax* 2013;**68**:611-18. <http://dx.doi.org/10.1136/thoraxjnl-2012-201815>
- Global Initiative for Asthma (GINA). The Global Strategy for Asthma Management and Prevention, Updated 2012. Available from: <http://www.ginasthma.org> (accessed July 2013)
- British Thoracic Society/Scottish Intercollegiate Guidelines Network. *British Guideline on the Management of Asthma* 2008. *Thorax* 2008;**63**(Suppl 4): 1-121 Update 2012 available from: <http://www.brit-thoracic.org.uk> and <http://www.sign.ac.uk> (accessed July 2013)
- Pinnock H, Fletcher M, Holmes S, *et al*. Setting the standard for routine asthma consultations: a discussion of the aims, process and outcomes of reviewing people with asthma in primary care. *Prim Care Respir J* 2010;**19**:75-83. <http://dx.doi.org/10.4104/pcrj.2010.00006>
- Al-Jahdali H, Anwar A, Abdullah Al-H, *et al*. Improper inhaler technique is associated with poor asthma control and frequent emergency department visits. *Allergy, Asthma Clin Immunol* 2013;**9**:8. <http://dx.doi.org/10.1186/1710-1492-9-8>
- Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and

- repeat emergency department visits for adults with asthma. *Thorax* 2000; **55**:566-573. <http://dx.doi.org/10.1136/thorax.55.7.566>
18. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD000011. <http://dx.doi.org/10.1002/14651858.CD000011.pub3>
 19. Gamble J, Stevenson M, McClean E, Heaney LG. The Prevalence of Non-adherence in Difficult Asthma. *Am J Respir Crit Care Med* 2009; **180**:817-22. <http://dx.doi.org/10.1164/rccm.200902-0166OC>
 20. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; **343**:332-6. <http://dx.doi.org/10.1056/NEJM200008033430504>
 21. Bender B, Milgrom H, Rand C. Non-adherence in asthmatic patients: is there a solution to the problem? *Ann Allergy Asthma Immunol* 1997; **79**:177-18. [http://dx.doi.org/10.1016/S1081-1206\(10\)63001-3](http://dx.doi.org/10.1016/S1081-1206(10)63001-3)
 22. International Primary Care Respiratory Group. Difficult to manage asthma. Available from <http://www.theipcrj.org/display/DIFFMANAST/Home++Difficult+to+manage+asthma> (Accessed July 2013)
 23. Currie GP, Douglas JG, Heaney LG. Difficult to treat asthma in adults. *BMJ* 2009; **338**:593-7. <http://dx.doi.org/10.1136/bmj.b494>
 24. Pacheco-Galván A, Hart SP, Morice AH. Relationship between gastro-oesophageal reflux and airway diseases: the airway reflux paradigm. *Arch Bronconeumol* 2011; **47**:195-203. <http://dx.doi.org/10.1016/j.arbres.2011.02.001>
 25. Mastrorade JG, Anthonisen NR, Castro M, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 2009; **360**:1487-99. <http://dx.doi.org/10.1056/NEJMoa0806290>
 26. Brozek JL, Bousquet J, Baena-Cagnani CE et al. Global Allergy and Asthma European Network. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; **126**:466-76. <http://dx.doi.org/10.1016/j.jaci.2010.06.047>
 27. Fishwick D, Barber C, Walker S, Scott A. Asthma in the workplace: a case-based discussion and review of current evidence. *Prim Care Respir J* 2013; **22**:244-8. <http://dx.doi.org/10.4104/pcrj.2013.00038>
 28. Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001; **322**:1098-100. <http://dx.doi.org/10.1136/bmj.322.7294.1098>
 29. Bott J, Blumenthal S, Buxton M, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax* 2009; **64**(Suppl 1):i1-51. <http://dx.doi.org/10.1136/thx.2008.110726>
 30. Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians' 3 questions'. *Prim Care Respir J* 2009; **18**:83-8.
 31. Pinnock H, Burton C, Campbell S, et al. Clinical implications of the Royal College of Physicians three questions in routine asthma care: a real-life validation study. *Prim Care Respir J* 2012; **21**:288-94. <http://dx.doi.org/10.4104/pcrj.2012.00052>
 32. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; **113**:59-65. <http://dx.doi.org/10.1016/j.jaci.2003.09.008>
 33. Juniper EE, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006; **100**:616-21. <http://dx.doi.org/10.1016/j.rmed.2005.08.012>
 34. Azevedo P, Correia de Sousa J, Bousquet J, et al. in collaboration with the WHO Collaborative Center for Asthma and Rhinitis, Montpellier. Control of Allergic Rhinitis and Asthma Test (CARAT): dissemination and applications in primary care. *Prim Care Respir J* 2013; **22**:112-16. <http://dx.doi.org/10.4104/pcrj.2013.00012>
 35. Blakey JD, Woolnough K, Fellows J, Walker S, Thomas M, Pavord ID. Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm. *Prim Care Respir J* 2013; **22**(3):344-52. <http://dx.doi.org/10.4104/pcrj.2013.00063>
 36. James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 2007; **30**:134-55. <http://dx.doi.org/10.1183/09031936.00146905>
 37. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; **105**:930-8. <http://dx.doi.org/10.1016/j.rmed.2011.01.005>
 38. Molimard M, Gros VL. Impact of patient-related factors on asthma control. *J Asthma* 2008; **45**:109-13. <http://dx.doi.org/10.1080/02770900701815727>
 39. Capstick TG, Clifton IJ. Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. *Expert Rev Respir Med* 2012; **6**:91-101. <http://dx.doi.org/10.1586/ers.11.89>
 40. Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Care Respir J* 2009; **18**:243-9. <http://dx.doi.org/10.4104/pcrj.2009.00029>
 41. van der Wiel E, ten Hacken NH, Postma DS, van den Berge M. Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. *J Allergy Clin Immunol* 2013; **131**:646-57. <http://dx.doi.org/10.1016/j.jaci.2012.12.1567>
 42. Backer V, Bornemann M, Knudsen D, Ommen H. Scheduled asthma management in general practice generally improve asthma control in those who attend. *Respir Med* 2012; **106**:635-41. <http://dx.doi.org/10.1016/j.rmed.2012.01.005>
 43. National Institute for Health and Clinical Excellence. Quality standard 25, Asthma 2013. Available from <http://publications.nice.org.uk> (accessed July 2013)
 44. Ikeue T, Nakagawa A, Furuta K, et al. The prevalence of cigarette smoking among asthmatic adults and association of smoking with emergency department visits. *J Japanese Respir Soc* 2010; **48**:99-103.
 45. McLeish AC, Zvolensky MJ. Asthma and cigarette smoking: a review of the empirical literature. *J Asthma* 2010; **47**:345-61. <http://dx.doi.org/10.3109/02770900903556413>
 46. Self TH, Wallace JL, Gray LA, Usery JB, Finch CK, Deaton PR. Are we failing to document adequate smoking histories? A brief review 1999-2009. *Curr Med Res Opin* 2010; **26**:1691-6. <http://dx.doi.org/10.1185/03007995.2010.486574>
 47. To T, Daly C, Feldman R, McLimont S. Results from a community-based program evaluating the effect of changing smoking status on asthma symptom control. *BMC Public Health* 2012; **12**:293. <http://dx.doi.org/10.1186/1471-2458-12-293>
 48. Harmsen L, Gottlieb V, Rasmussen LM, Backer V. Asthma patients who smoke have signs of chronic airflow limitation before age 45. *J Asthma* 2010; **47**:362-6. <http://dx.doi.org/10.3109/02770901003692819>
 49. Slama KJ, Redman S, Cockburn J. Community views about the role of general practitioners in disease prevention. *Fam Pract* 1989; **6**:203-09. <http://dx.doi.org/10.1093/fampra/6.3.203>
 50. Brusselle G, Peché R, van den Brande P, Verhulst A, Hollanders W, Bruhwyler J. Real-life effectiveness of extrafine beclomethasone dipropionate/formoterol in adults with persistent asthma according to smoking status. *Respir Med* 2012; **106**:811-19. <http://dx.doi.org/10.1016/j.rmed.2012.01.010>
 51. Thomson NC, Spears M. Asthma guidelines and smokers: it's time to be inclusive. *Chest* 2012; **141**:286-8. <http://dx.doi.org/10.1378/chest.11-1424>
 52. Price D, Popov TA, Bjermer L, et al. Effect of montelukast for treatment of asthma in cigarette smokers. *J Allergy Clin Immunol* 2013; **131**:763-71. <http://dx.doi.org/10.1016/j.jaci.2012.12.673>
 53. Ahmad Z, Singh SK. Relative and additional bronchodilator response of salbutamol and ipratropium in smoker and nonsmoker asthmatics. *J Asthma* 2010; **47**:340-3. <http://dx.doi.org/10.3109/02770900903584456>
 54. de Groene GJ, Pal TM, Beach J, et al. Workplace interventions for treatment of occupational asthma. *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No.: CD006308. <http://dx.doi.org/10.1002/14651858.CD006308.pub3>
 55. Leander M, Lampa E, Janson C, Svärdsudd K, Uddenfeldt M, Rask-Andersen A. Determinants for a low health-related quality of life in asthmatics. *Uppsala J Med Sciences* 2012; **117**:57-66. <http://dx.doi.org/10.3109/03009734.2011.638730>
 56. Heaney LG, Conway E, Kelly C, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003; **58**:561-56. <http://dx.doi.org/10.1136/thorax.58.7.561>
 57. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Asthma and Allergy Research Group of the National Heart and Lung Institute. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; **22**:478-83. <http://dx.doi.org/10.1183/09031936.03.00017003>
 58. American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000; **162**:2341-51. <http://dx.doi.org/10.1164/ajrccm.162.6.ats9-00>
 59. Bel EH, Sousa A, Fleming L, for U-BIOPRED Consortium, Consensus Generation. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011; **66**:910-17. <http://dx.doi.org/10.1136/thx.2010.153643>
 60. Hamelmann E. The rationale for treating allergic asthma with anti-IgE. *Eur Respir Rev* 2007; **16**:61-6. <http://dx.doi.org/10.1183/09059180.00010401>

61. Kerstjens HA, Engel M, Dahl R, *et al.* Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;**367**:1198-207. <http://dx.doi.org/10.1056/NEJMoa1208606>
62. Cox PG, Miller J, Mitzner W, Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. *Eur Respir J* 2004;**24**:659-63. <http://dx.doi.org/10.1183/09031936.04.00054604>
63. Castro M, Rubin AS, Lavolette M, *et al.* Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma: A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial. *Am J Respir Crit Care Med* 2010;**181**:116-24. <http://dx.doi.org/10.1164/rccm.200903-0354OC>
64. Corren J, Lemanske RF, Hanania NA, *et al.* Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;**365**:1088-98. <http://dx.doi.org/10.1056/NEJMoa1106469>
65. Pavord ID, Korn S, Howarth P, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;**380**:651-9. [http://dx.doi.org/10.1016/S0140-6736\(12\)60988-X](http://dx.doi.org/10.1016/S0140-6736(12)60988-X)
66. Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;**368**:2455-66. <http://dx.doi.org/10.1056/NEJMoa1304048>
67. Holgate ST. Asthma: a simple concept but in reality a complex disease. *Eur J Clin Invest* 2011;**41**:1339-52. <http://dx.doi.org/10.1111/j.1365-2362.2011.02534.x>
68. Wark P, Gibson PG, Wilson A. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database of Systematic Reviews* 2004(3): Art. No.: CD001108. <http://dx.doi.org/10.1002/14651858.CD001108.pub2>
69. Denning DW, O'Driscoll BR, Powell G, *et al.* Randomized Controlled Trial of Oral Antifungal Treatment for Severe Asthma with Fungal Sensitization: The Fungal Asthma Sensitization Trial (FAST) Study. *Am J Respir Crit Care Med* 2009;**179**:11-18. <http://dx.doi.org/10.1164/rccm.200805-737OC>
70. Lazarus SC, Chinchilli VM, Rollings NJ, *et al.* Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;**175**:783-90. <http://dx.doi.org/10.1164/rccm.200511-1746OC>
71. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002;**19**:246-51. <http://dx.doi.org/10.1183/09031936.02.00218402>
72. Crompton GK, Barnes PJ, Broeders M, *et al.* The need to improve inhalation technique in Europe: A report from the Aerosol Drug Management Improvement Team. *Respir Med* 2006;**100**:1479-94. <http://dx.doi.org/10.1016/j.rmed.2006.01.008>
73. Mulloy E, Donaghy D, Quigley C, McNicholas WT. A one-year prospective audit of an asthma education programme in an out-patient setting. *Ir Med J* 1996;**89**:226-8.
74. Plaza V, Sanchis J, Roura P, *et al.* Physicians' knowledge of inhaler devices and inhalation techniques remains poor in Spain. *J Aerosol Med Pulm Drug Deliv* 2012;**25**:16-22. <http://dx.doi.org/10.1089/jamp.2011.0895>
75. Hanania NA, Wittman R, Kesten S, Chapman KR. Medical personnel's knowledge of and ability to use inhaling devices. *Chest* 1994;**105**:111-16. <http://dx.doi.org/10.1378/chest.105.1.111>
76. Plaza V, Sanchis J. Medical personnel and patient skill in the use of metered dose inhalers: a multicentre study. CESEA Group. *Respiration* 1998;**6**:195-8. <http://dx.doi.org/10.1159/000029259>
77. van der Palen J, Klein JJ, van Herwaarden CL, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. *Eur Respir J* 1999;**14**:1034-7. <http://dx.doi.org/10.1183/09031936.99.14510349>
78. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax* 2004;**59**:94-99. <http://dx.doi.org/10.1136/thorax.2003.011858>
79. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis. *Arch Intern Med* 1999;**159**:941-55. <http://dx.doi.org/10.1001/archinte.159.9.941>
80. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med* 2010;**123**:1001-06. <http://dx.doi.org/10.1016/j.amjmed.2010.06.019>
81. Salpeter MD, Buckley NS, Ormiston TM, Salpeter EE. Meta-Analysis: Effect of Long-Acting β -Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths. *Ann Intern Med* 2006;**144**:904-12. <http://dx.doi.org/10.7326/0003-4819-144-12-200606200-00126>

Available online at <http://www.thepcrj.org>

The IPCRG launches a set of resources on Difficult to Manage Asthma at the ERS Primary Care Day 7 September 2013



- Desktop helper for primary care clinicians in 9 languages
- Policy paper for local, national and pan-national policy-makers making the case for investment to achieve better value in healthcare
- Video demonstrating an asthma review using SIMPLES a mnemonic explained in the desktop helper
- A collection of additional free online resources and references

<https://www.theipcr.org/display/DIFFMANAST/Home+-+Difficult+to+manage+asthma>