

GUIDELINES FOR THE MANAGEMENT OF ADULT ASTHMA

**Approved by the Winchester & Southampton District
Prescribing Committee**

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KEY MESSAGES

- Engage the patient as a willing partner – encourage self-management plans.
- **Use asthma therapy to gain “asthma control”.**
- **Adopt a stepwise approach to asthma therapy.**
- **Do not skip steps.**
- **At all steps ensure good education, compliance & inhaler technique.**
- **STEP UP** to gain & maintain control.
- **STEP DOWN** if well controlled.
- If asthma is not controlled look for a reason! Characterise asthma – ask “what is driving this patient’s asthma?” Consider comorbidities & treat.
- **STEP 1:**
Start with a short-acting β -agonist when needed (**anticholinergics are not usually indicated in asthma**).
- **STEP 2:**
 - ✓ Add in low dose inhaled steroid if uncontrolled. Prescribe CFC-free Beclometasone (BDP) by brand (either Clenil Modulite or Qvar) to avoid confusion.
 - ✓ Clenil is dose equivalent to CFC-BDP.
 - ✓ **If using Qvar, prescribe at ½ dose of other BDP preparations.**
 - ✓ Use ultrafine BDP (QVAR) if uncontrolled on alternatives prior to stepping up.
 - ✓ **Never** use long acting β -agonist (LABA) or leukotriene antagonist (LTRA) as monotherapy.
- **STEP 3:**
 - ✓ Consider **choices of add-on therapy** (LABA or LTRA) to inhaled steroid.
 - ✓ Tailor choice to patient.
 - ✓ **Montelukast** is 1st line LTRA.
 - ✓ **Formoterol (Atimos Modulite)** is 1st line LABA.
 - ✓ Assess efficacy of therapeutic changes after a two month trial.
 - ✓ If a LABA is effective consider using a Formoterol containing combination inhaler to aid compliance if appropriate.
 - ✓ Consider using Symbicort as **“Single Inhaler as Maintenance & Reliever” if deemed appropriate.**
 - ✓ If not controlled at step 3 refer to a Specialist.
- **STEPS 4 & 5:**
Patient care should be supervised by a Specialist.
- **EXACERBATIONS:**
 - ✓ After any exacerbation ask “why has this patient lost asthma control?”
 - ✓ Ensure that all patients are on inhaled steroid post exacerbation.
 - ✓ Follow-up patients post exacerbation to ensure “control” regained.

INTRODUCTION

Asthma prevalence in the United Kingdom showed a steady increase over the final decades of the 20th Century and it has only recently begun to plateau. It is estimated that there are just over 5 million asthmatics in the UK today. The direct health economic impact of this common disease through healthcare needs is considerable. However there is also a considerable unappreciated societal burden created by associated disability, lost working days and impaired schooling. Recent data shows that:

- One in 5 UK households possesses an asthmatic individual.
- Asthma accounts for an estimated 12.7 million lost working days per year.
- In 2005 there were 77,000 UK asthma related hospital admissions.
- It is estimated that 75% asthma admissions are potentially preventable.
- In 2004 there were 1381 UK asthma related deaths.
- On average there is one asthma related death every 8 hours in the UK.
- Asthma/COPD medications account for over 80% UK respiratory drug expenditure.
- UK Asthma related health expenditure is estimated at £996 million/year.
- At any point in time 20% of the UK asthma population has “difficult to treat” or “refractory” disease.
- It is estimated that “difficult to treat” disease accounts for >80% of UK asthma related health expenditure (direct and indirect costs).

This Guideline offers a structured approach for the care of adult asthmatic patients, covering the spectrum of Primary and Secondary Care within our locality, placing expert opinion plus recent National (BTS/NICE) and International (GINA) Recommendations within a local context.

The aim of this Guideline is to ultimately achieve better management of this common condition in our Community. To achieve this goal the notion of establishing “asthma control” is strongly emphasised, as outlined by the GINA (Global Initiative for Asthma) 2006 Update.

The Guideline provides a core diagnostic pathway. It goes on to explain the concept of assessing asthma control, treating to establish control and monitoring to maintain control. The importance of “stepping down” therapy when stable is described. A treatment algorithm is defined that allows a logical approach to asthma management that can be individually tailored to the patients’ disease. In particular, potential strategies at Step 3 are described in detail. New concepts such as “Single inhaler as Maintenance & Reliever Therapy” (SMART) and “One Airway-One Disease” are explained. A “holistic” approach that looks beyond “just asthma” is encouraged and explained. Emphasis on self-management is made, including “asthma action plans”, to facilitate a successful patient-carer relationship. The Guideline goes on to provide guidance on management of acute exacerbations. Information on costs of therapy is also provided. Finally a list of useful contacts and learning resources (BTS, NICE, GINA) are included at the end of the document.

We hope that this document proves a useful tool to improve the experience of the local asthma patient. A revision will be undertaken in 2010.

DIAGNOSIS & INVESTIGATIONS

“Asthma is a chronic inflammatory disorder of the airways in which many inflammatory cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.”

The diagnosis of asthma is a clinical one, often made problematic by the lack of a simple or clear definition of what asthma actually is. It is important to remember that no single test can prove diagnostic for asthma. A secure diagnosis is based upon the principles of taking a thorough history, making a relevant physical examination of the chest and nose, and performing relevant tests as directed by the individual patients' presentation.

Important steps in the initial diagnosis of asthma are outlined in the accompanying table.

The differential diagnosis of asthma (see below) is wide and consideration should be given to a variety of conditions depending upon individual circumstances. More than one condition may co-exist within the same individual. **In situations of diagnostic doubt early specialist review is encouraged.**

Differential Diagnosis:

- COPD
- Bronchiectasis
- Cystic Fibrosis
- Tumour
- Foreign body
- Interstitial lung disease
- Pulmonary emboli
- Aspiration
- Vocal cord dysfunction
- Hyperventilation syndrome
- Cardiac disease

Asthma v COPD:

The differentiation of asthma from Chronic Obstructive Pulmonary Disease (COPD) is important since there are key differences in therapeutic approaches to these common airway diseases.

COPD is rare below the age of 35 years and in the absence of a smoking history, so be wary of making that diagnosis in those circumstances. COPD is usually associated with chronic generally progressive symptoms as opposed to the characteristically variable pattern seen most commonly in asthma. Furthermore asthma often occurs in the setting of allergic comorbidities (eg rhinitis) and asthmatic family history. Objective tests such as Peak Expiratory Flow monitoring or spirometry with bronchodilator or corticosteroid reversibility can help by demonstrating fixed airflow obstruction (COPD) or variability/ reversibility (asthma). Finally it should be noted that COPD and asthma can coexist in the same patient.

ASTHMA DIAGNOSIS & INVESTIGATIONS

SYMPTOMS	SIGNS
Episodic/variable: <ul style="list-style-type: none"> • Wheeze • Breathlessness • Chest tightness • Cough • Mucus production 	<ul style="list-style-type: none"> • None (common) • Wheeze – diffuse, bilateral, expiratory (+/- inspiratory) • Tachypnoea • Nasal disease
<u>Other Important Information:</u>	
<ul style="list-style-type: none"> • Personal or family history of asthma/atopy (eczema, rhinitis, food allergy). • Recognised triggers – pollens, dust, animals, foods, medications, exercise, viral infections, chemicals, irritants. • History of symptom worsening with aspirin/NSAIDs/ β-blockers. • Occupation. • Smoking history. 	
<u>Objective Measurements</u>	
<ul style="list-style-type: none"> • > 20% diurnal variation on ≥ 3 days in a week for 2 weeks on Peak Expiratory Flow (PEF) diary. • FEV₁ $\geq 15\%$ (and 200 ml) increase after short acting β-agonist (eg salbutamol 400 micrograms by pMDI/spacer or 2.5 milligrams by nebuliser). • FEV₁ $\geq 15\%$ (and 200 ml) increase after 14 DAY Prednisolone trial (30milligrams/day). • FEV₁ $\geq 15\%$ decrease after strenuous exercise (running). 	
<u>Indications for Specialist Opinion:</u> <ul style="list-style-type: none"> • Diagnostic doubt • Poor treatment response • STEP 4 of asthma therapy • Unexpected clinical findings (eg crackles, clubbing, cyanosis, heart failure) • Spirometry/PEF don't match clinical picture • Suspected occupational asthma • Persistent breathlessness (not episodic or without wheeze) • Unilateral or fixed wheeze • Stridor • Persistent chest pain • Weight loss • Persistent cough/ sputum • Non-resolving pneumonia 	<u>Consider the Following Specialist Tests in Individual Cases:</u> <ul style="list-style-type: none"> • Chest x-ray • Full pulmonary function tests • Full blood count • Total IgE • Skin prick test to common aeroallergens • Specific IgE to Aspergillus • Aspergillus precipitins • Immunoglobulins • Alpha-1-antitrypsin levels • ANCA • Sputum for fungal stains • HRCT Chest • Histamine bronchial challenge • Exhaled nitric oxide • Bronchoscopy plus biopsy/lavage

THE CONCEPT OF CONTROL

The goal of any asthma management strategy should be to establish and maintain disease control using the lowest effective dose of medication. Central to this aim is a good patient-carer relationship that engages the patient as a willing and knowledgeable partner. In turn, opportunities should always be sought to enhance patients understanding of their asthma.

In most cases asthma control can be achieved using conventional pharmacological agents under the guidance of a healthcare professional. To realise that aim there needs to be a continual process that includes assessment of control, applies appropriate therapy to gain control and finally encourages monitoring (by patient and healthcare professional) to maintain control at lowest effective doses of therapy.

Assessment of Control:

Each patient should be assessed as to their adherence with, and ability to correctly take, current treatment as well as their corresponding asthma control. Asthma control can be defined as “Controlled”, “Partially Controlled” or “Uncontrolled” as outlined in the table below.

DEFINING ASTHMA CONTROL

	CONTROLLED (All of the following)	PARTIALLY CONTROLLED (Any measure present in any week)	UNCONTROLLED
Daytime Symptoms	None (twice or less weekly)	More than twice weekly	3 or more features of partly controlled asthma present in any week.
Limitation of activity	None	Any	
Nocturnal Symptoms	None	Any	
Reliever medication	None (twice or less weekly)	More than twice weekly	
Lung function.	Normal	<80% personal best or predicted	
Exacerbation	None	Any in past year	
ACTION	MAINTAIN CONTROL & FIND LOWEST CONTROLLING STEP	CONSIDER STEPPING UP TO GAIN CONTROL	STEP UP UNTIL CONTROLLED & TREAT ANY EXACERBATION

Ideally the patient should be actively engaged in the process of monitoring their asthma control thereby placing them “in control” of their own disease. A simple questionnaire tool can be used to aid that process, ideally as part of a Written Asthma Action Plan (see later). An example of a simple asthma control questionnaire is given below.

Asthma Control Questionnaire:

1. *Has your asthma awakened you at night?*
2. *Have you needed more reliever medications than usual?*
3. *Have you required urgent medical review?*
4. *Has your peak flow been below your personal best?*
5. *Are you participating in your usual activities?*

Treating to Achieve Control:

A stepwise approach to asthma management is recommended using a 5 Step Treatment Strategy (See Algorithm). The aim of this strategy is to essentially control symptoms by controlling the causative underlying airway inflammation. **Loss of asthma control should always prompt a search as to why that has happened.**

In treatment naïve cases with only intermittent symptoms treatment should be begun with as needed reliever only (Step 1). In treatment naïve cases with persistently symptomatic asthma therapy should commence with regular controller therapy in the form of inhaled glucocorticosteroid (ICS - Step 2). If control remains suboptimal then it should be “stepped up” and reviewed repeatedly to assess for achievement of control (Steps 3-5). It should be noted that at least 2 months should be allowed to judge efficacy of any new controller therapy (longer if more severe disease). ***Starting therapy straight at Step 3 is only indicated in severe uncontrolled asthma.*** If stable control is established for 3-6 months, “stepping down” should always be considered with continued assessment of control. **The nature of and reasons for, treatment changes should always be clearly explained to the patient.**

Monitoring to Maintain Control & Stepping Down:

When asthma is controlled, ongoing monitoring is essential to maintain control and establish the lowest step and dose of treatment needed, maximising safety and minimising cost. However, asthma is a variable disease, and therapy will need to be periodically adjusted in response to loss of control.

Monitoring should be done by both healthcare professional and patients using tools as detailed above. Ideally this process should be linked to tools such as written asthma action plans that help informed patients take more control of their own health.

There is limited data on “stepping down” strategies and further research is required in this area. However as outlined in GINA 2006;

- When ICS are used alone in medium-high dose, a 50% reduction in dose can be attempted at 3 monthly intervals.
- Where control is achieved by low dose ICS alone, in most cases treatment may be switched to once-daily dosing.
- When asthma is controlled with a combination of ICS and long acting β -agonist (LABA), the preferred approach is to initially reduce the ICS dose by 50% whilst continuing the LABA. If controlled, further reduction in ICS dose until low-dose is reached can be tried followed by withdrawal of LABA if still stable. An alternative strategy is to reduce combination therapy to once-daily dosing.
- When asthma is controlled by ICS plus controllers other than LABA's, the ICS dose should be reduced by 50% until low-dose is achieved. If still stable then withdrawal of the controller can be attempted.
- Controller treatment can be discontinued if the asthma is controlled on low-dose ICS with no recurrence of symptoms for more than 12 months.

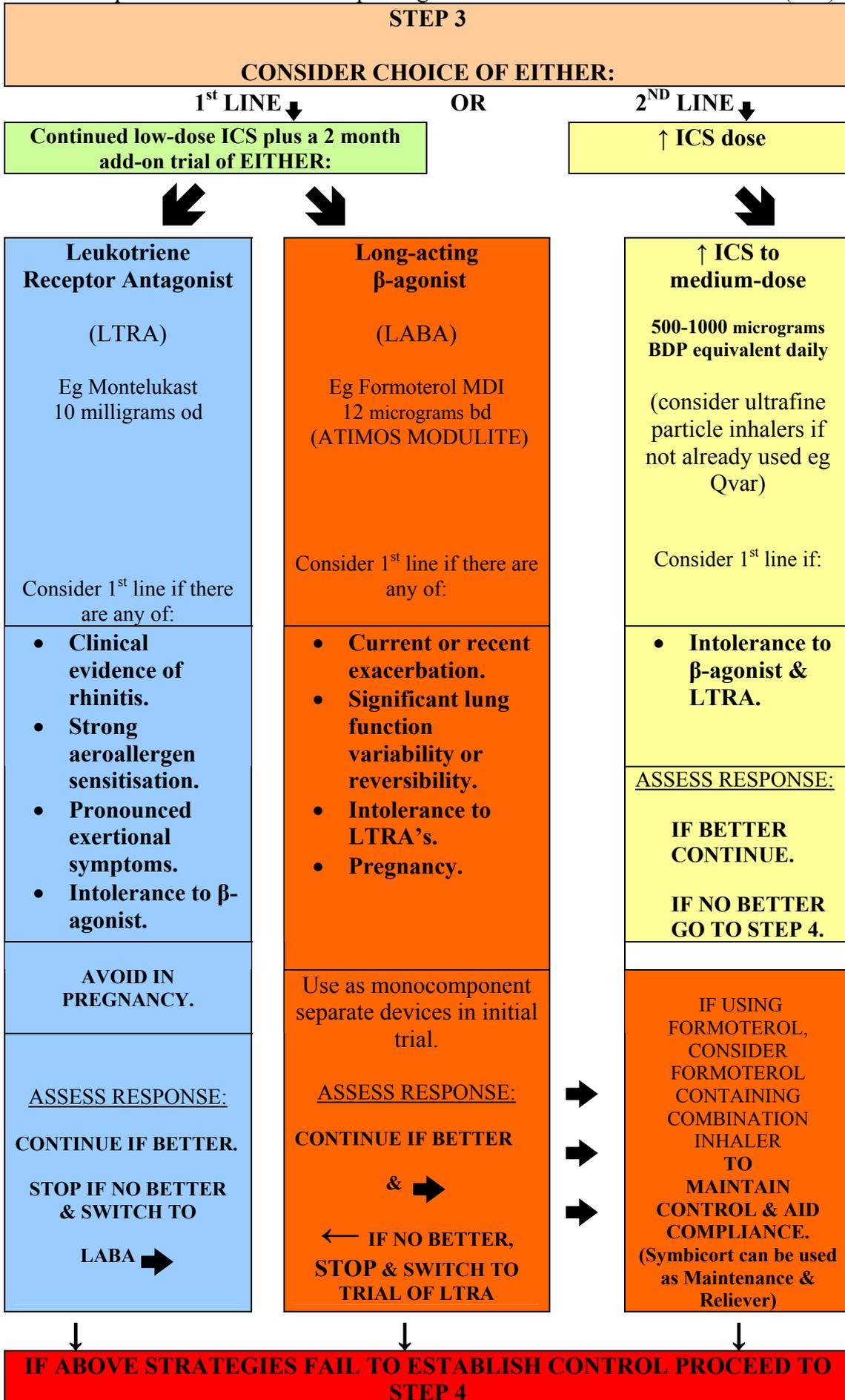
SOUTHAMPTON ADULT ASTHMA MANAGEMENT ALGORITHM

AT ALL STEPS				
Ensure good inhaler technique, compliance and patient education before moving up a step				
Actively encourage smoking cessation and physical activity				
Advise on allergen avoidance where relevant				
Offer annual Influenza vaccination				
STEP 1 ↔	↔STEP 2↔	↔STEP 3↔	↔STEP 4↔	↔STEP 5
As needed short acting β-agonist	<p>As needed short acting β-agonist (eg Salbutamol 200micrograms) PLUS REGULAR CONTROLLER THERAPY</p> <p style="text-align: center;">↑ STEP UP TO GAIN & MAINTAIN CONTROL ↓ ONCE CONTROLLED AIM TO STEP DOWN AS TOLERATED</p>			
CONTROLLER OPTIONS	↔STEP 2↔	↔STEP 3↔	↔STEP 4↔	↔STEP 5
	<p>LOW-DOSE INHALED STEROID (ICS)</p> <p>200-500 micrograms daily Conventional Beclometasone (BDP) equivalent</p> <p>Prescribe by brand:</p> <p>Clenil Modulite (CFC-free BDP) is dose equivalent to CFC-BDP & is suitable for switching at Step 2 for many primary care patients.</p> <p>or</p> <p>Qvar (ultrafine CFC-free BDP) is an alternative option at half CFC-BDP dose.</p>	<p>CHOOSE A 2 MONTH TRIAL OF :</p> <p>Low-dose ICS + either Long-acting β-agonist (LABA) Or Leukotriene Receptor Antagonist (LTRA)</p> <p style="text-align: center;">OR</p> <p>↑ ICS to medium-dose 500-1000 micrograms daily BDP equivalent (Try Qvar if not already used)</p> <p>[See Step 3 of choices]</p>	<p>SPECIALIST REVIEW SUGGESTED & USE:</p> <p>Medium-high dose ICS 500-2000 micrograms daily BDP equivalent (Try Qvar if not already used)</p> <p style="text-align: center;">+</p> <p>SEQUENTIALLY ADD ONE OR MORE OF:</p> <p>LABA Or LTRA Or Sustained release theophyllines</p> <p>With review of response at 2 month intervals to assess efficacy & control</p>	<p>UNDER SPECIALIST GUIDANCE CONSIDER ADDITION OF:</p> <p>ORAL CORTICOSTEROID MAINTENANCE THERAPY* (lowest controlling dose)</p> <p style="text-align: center;">Or</p> <p>ORAL STEROID SPARING AGENTS</p> <p style="text-align: center;">Or</p> <p>DISEASE MODIFYING INJECTION THERAPIES</p> <p style="text-align: center;">+/- Nebuliser Therapy</p> <p>*Assess Bone Mineral Density</p>
	CONSIDER & TREAT IF PRESENT AT ANY STAGE:			
RHINITIS, GASTRO-OESOPHAGEAL REFLUX, BRONCHIECTASIS, OBSTRUCTIVE SLEEP APNOEA, DYSFUNCTIONAL BREATHING, PSYCHOLOGICAL DYSFUNCTION				

Treatment changes should be made on a trial basis with review of efficacy

STEP 3 OF CHOICES

Inadequate Asthma Control despite regular low dose Inhaled Corticosteroid (ICS)



THE ALGORITHMS EXPLAINED

Achieving control is the cornerstone of proper asthma management. In persistent disease this is achieved by the early use of anti-inflammatory therapies that tackle the underlying pathophysiology of this disease. **Inhaled glucocorticosteroids therefore have a crucial early role.** Such pharmacological therapy is ancillary to non-pharmacological measures including patient education, smoking cessation, annual influenza vaccination, allergen avoidance, psychological support and physiotherapy input; all of which may have utility in individual cases.

The Southampton Adult Asthma Algorithm offers an evidence based strategy to manage asthma. Further details of the Algorithm are given below.

i. General Measures:

- Check that the patient can use the inhaler device properly prior to prescription; recheck technique at each review.
- A pressurised Meter Dose Inhaler (pMDI) should usually be prescribed with a spacer device. A Volumatic is first choice in this regard, unless prescribing QVAR which only fits the aerochamber device.
- Always assess compliance.
- Ideally provide the patient with a written Asthma Action Plan.
- Nebuliser therapy is no more effective than inhaled therapy and should be regarded as a “last resort” option after assessment in Secondary Care.
- Physical activity should always be encouraged – consider “Active Options” in selected cases.
- **Referral for assessment in Secondary Care can occur at any stage but is DEFINITELY ADVISABLE ONCE THE PATIENT IS INADEQUATELY CONTROLLED AT STEP 3!!!**

ii. Smoking Cessation:

Smoking cessation is an important component of asthma therapy. There is clear evidence of reduced efficacy of treatment such as inhaled corticosteroids¹ in asthmatics who smoke. Asthmatics may also carry increased risk of developing COPD²⁻³, for which cigarette smoking is the main risk factor.

In order to address this issue, health professionals should;

1. *ASK* all patients about their smoking history.
2. *ADVISE* all patients to quit using personalised but non-judgemental language.
3. *ASSESS* motivation to quit smoking.
4. *ASSIST* motivated smokers by issuing further advice and prescribing NRT (Nicotine Replacement Therapy) or bupropion.
5. *ARRANGE* support follow up with “Quitters” (SCPCT) or “Quit4Life” (Hampshire PCT).

iii. Drugs:

➤ Inhaled Corticosteroids (ICS):

ICS should be started at low-dose (Step 2) in any partially controlled or uncontrolled steroid naïve asthmatic. *It is especially important to remember this point in previously controlled steroid naïve patients recovering from an exacerbation.* In this context low-dose means 200-500 micrograms conventional Beclometasone (BDP) equivalent. Prescribe by brand to avoid confusion. Clenil Modulite (CFC-free MDI) is suitable for many patients at Step 2 and is dose equivalent to CFC-BDP.

➤ **Ultra-fine Particle ICS:**

It should be noted that some HFA solution preparations of ICS such as QVAR, which generate ultra-fine particles, offer superior lung deposition (up to 50%) with improved penetration to the peripheral airways and reduced oropharyngeal side-effects, thus allowing disease control at a reduced steroid dose. These can be considered at Step 2 in appropriate doses – **prescribe by brand at half dose of other BDP forms**. Qvar is available at doses of 50 and 100 micrograms strength, which are respectively equivalent to 100, and 200 micrograms of CFC-BDP and Clenil Modulite. Use ultrafine BDP (QVAR) if uncontrolled on alternatives prior to stepping up.

➤ **Early Characterisation of Asthma:**

Early characterisation of asthma describes the process of identifying relevant aggravating factors and comorbidities that are driving the asthmatic process. This is crucial to the concept of tailoring asthma therapy to the individual patient.

➤ **Step 3 of Choices:**

- Check good compliance and proper inhaler technique at Step 2 before moving to Step 3.
- Step 3 is a stage where choice of asthma therapy can be tailored to the individual patient, dependent on their characteristics and preference.
- Generally addition of a second controller at this stage (**Leukotriene Receptor Antagonist**⁴ {LTRA} or **Long Acting β -Agonist**⁵ {LABA}) is recommended in preference to simply increasing dose of ICS.
- Treatment should be initiated for a trial of at least 2 months.
- **NEITHER LABA NOR LTRA SHOULD BE USED AS MONOTHERAPY FOR ASTHMA.**
- Strong indications to try LTRA 1st line include coexistent rhinitis⁶, aeroallergen sensitisation or exertional symptoms – see “One Airway-One Disease”.
- LTRA should NOT be initiated during pregnancy.
- Strong indications to try LABA 1st line include current or recent exacerbation, significant disease variability / reversibility, disabling symptoms or pregnancy. Use **Formoterol (Atimos Modulite)** MDI 12 micrograms bd 1st line (full β -receptor agonist).
- **If LABA is effective and using Formoterol, consider switching to a Formoterol containing combination inhaler to aid compliance if appropriate.** If a combination device, rather than separate inhalers, is chosen then the least costly device suitable for the individual is recommended [NICE – “Asthma (in adults) –corticosteroids” (*NICE technology appraisal guidance 138* – www.nice.org.uk/TA138)].
- Symbicort can be used as maintenance and reliever (see “Single Inhaler as Maintenance & Reliever Therapy”) if appropriate.
- If partial improvement in disease control occurs then continue either LTRA or LABA and increase the ICS dose (consider ultra-fine HFA preparations such as QVAR if not already used).
- Where neither LABA nor LTRA are tolerated increase ICS dose but consider ultra-fine HFA solution preparations such as QVAR if not already used.

➤ **Steroid Inhaler Equivalence:**

CFC-BDP (eg Becotide), CFC-free BDP (eg Clenil), and Budesonide (eg Pulmicort) are approximately dose equivalent in clinical practice. Fluticasone (eg Flixotide) and CFC-free ultrafine BDP (eg Qvar) are effective at approximately half the dose of CFC-BDP, Clenil and Budesonide.

➤ **Combination Inhalers:**

- Symbicort contains Budesonide (Pulmicort) & Formoterol (Oxis).
- Fostair contains CFC-free ultrafine BDP & Atimos Modulite (Formoterol).
- Seretide (Non-Formulary) contains Fluticasone (Flixotide) & Salmeterol (Serevent).

➤ **Single Inhaler as Maintenance & Reliever Therapy (SMART):**

The LABA **Formoterol** is a full β -receptor agonist with a rapid onset of action plus lack of tolerance that enables repeated dosing. These properties mean that it can be used repeatedly to relieve acute bronchoconstriction. Whilst the synergism of ICS and LABA in asthma therapy is well established, recent work⁷⁻⁹ has shown efficacy for combinations containing ICS & Formoterol in the relief of acute symptoms. Thus added reliever use of Formoterol/ICS combinations has been shown to reduce severe exacerbation rates, improve symptom control, reduce reliever therapy use and lower overall steroid load. Use of Symbicort (Budesonide/Formoterol) as both maintenance and reliever therapy has now been licensed in the UK. Guidelines for this technique are as follows;

- Take an extra dose of combination inhaler if symptomatic. If no relief after 10 minutes the patient can repeat up to a maximum extra 6 doses at 10 minute intervals until symptom relief is obtained. If no relief at that point medical review is needed.
- A maximum of 8 extra doses is permitted per 24 hours (making a total of 12 doses with conventional maintenance therapy).
- If symptoms persist despite this strategy medical review is needed.

➤ **Step 4:**

- At this stage, specialist assessment is indicated if not already obtained.
- Increase ICS to medium-high doses in conjunction with sequential addition of further controller medication.
- Proper characterisation of aggravating factors and comorbidities should be conducted at this stage.

➤ **Starting Theophyllines:**

- These agents are indicated at Step 4.
- Check BNF for drug interactions.
- Check theophylline blood level after one week to ensure therapeutic.
- Discontinue after 1 month if no symptomatic improvement with therapeutic blood levels.
- Repeat levels if smoking status changes, liver disease or cardiac failure present or commences/stops a drug that interacts with theophyllines.

➤ **Step 5:**

Specialist management is mandatory for this “difficult to treat” end of the asthma spectrum. Comorbidities should be reviewed for their influence on asthma control. Treatment goals remain optimal control with least side-effects, though potent therapies with significant potential side-effects, like oral corticosteroids or steroid

sparing agents, may be required. At this step, “off-licence” use of drugs may be needed under specialist guidance. For example continuous subcutaneous infusions of terbutaline¹⁰ have a recognised role in some cases. The new injected anti-IgE controller therapy (Omalizumab)¹¹, has been approved by The National Institute for Clinical Excellence for use in severe asthma under expert guidance (www.nice.org.uk/TA133) and may have a role in a few patients at this stage. The DPC recently agreed this should be by specialist prescription only (i.e ‘red’ drug).

iv. Allergen avoidance advice:

Allergen avoidance measures can be helpful in individual cases where atopic sensitisation exists. Such measures are not a substitute for pharmacological therapy. **Single measures are unlikely to be useful in isolation** but some benefit may be obtained through use of multiple measures in individual cases. Allergen avoidance recommendations for house dust mite, pets and pollens are given in Appendix II.

v. Risks of Osteoporosis – Screening & Therapy:

Asthmatic patients on high-dose ICS or oral glucocorticosteroids at any dose are considered at risk of developing osteoporosis and fractures, but it is not certain whether this risk exists for patients on lower doses of ICS. At risk patients should be considered for monitoring of osteoporosis on an individual basis. Appendix III details local advice¹² for monitoring and managing steroid induced osteoporosis.

WHAT ABOUT DIFFICULT ASTHMA?

In most asthmatics, the above management strategy will deliver optimal disease control. However in some patients asthma may prove “difficult” to control. In such cases in the first instance it is worth considering the following questions:

■ **Is it asthma?**

Consider the wide differential diagnosis outlined previously. It is also always worth considering the possibility that the patient may have asthma + another disease!!

■ **If it is asthma, is compliance good?**

■ **If it is asthma, is inhaler technique good?**

■ **If it is asthma, are there complicating factors?**

In difficult asthma, it is always worth considering the presence of specific complicating factors as listed under specific considerations – characterisation¹³ is crucial.

SPECIFIC CONSIDERATIONS

One Airway-One Disease:

Always inspect the nose in a patient with asthma. Co-existent rhinitis is a frequent finding in asthma (“one airway-one disease”) and treatment of that component of disease may help improve asthma control¹⁴. If detected, rhinitis should be actively treated. LTRA’S may offer a convenient add-on therapy to ICS that treats both upper and lower airway inflammation. Other rhinitis treatments to consider include regular antihistamines, nasal steroids, and consideration of allergen avoidance measures if appropriate.

Atopy:

Allergen exposure is a potent trigger in atopic asthma and rhinitis. The atopic status of a poorly controlled asthmatic should be defined by skin prick testing to a minimum panel of house dust mite, grass pollen, cat, tree pollen and aspergillus.

Salicylate Sensitivity:

Up to 20% of patients with difficult asthma may have a degree of salicylate sensitivity. This is typically found in association with a non atopic profile, persistent rhinitis and nasal polyposis. Urticaria and angioedema may also occur. Dietary salicylate exposure can be sufficient to cause problems and cross reactivity to sulphites may be seen. Such disease is often “treatment resistant”. Management options include aspirin/NSAID avoidance, leukotriene receptor antagonists and salicylate free diets. Specialist review is strongly advised for this form of disease.

Gastro-Oesophageal Reflux Disease (GORD):

GORD is a common clinical problem and asthmatics are estimated to have a 3-fold increased frequency of that condition. Medical therapy and lifestyle measures aimed at acid suppression/ reducing reflux can be helpful in improving asthma control in individual cases.

Drugs:

Certain drugs such as beta-blockers (including topical ocular preparations), NSAIDs and aspirin may worsen asthma control and should be screened for.

Dysfunctional Breathing:

This may be found in up to 40% of asthmatics and management through “breathing control training” can lead to significantly improved symptom control in individual cases. Close supervision by a chest physiotherapist is essential to educate and train the patient in this regard.

Vocal Cord Dysfunction:

Abnormal vocal cord function leading to inspiratory/expiratory airflow obstruction and acute breathlessness may be present in 20-40% of patients with difficult asthma. Multiple

potential contributing factors have been postulated including rhinitis, GORD and psychological stress. Treatment may be difficult and a multidisciplinary approach addressing causes and involving a wider “team” including speech therapists and physiotherapists carries the best hope of success.

Psychological Stress:

This is a common finding in severe asthma and also a poor prognostic marker which may significantly impair disease control. Where present the causes of this should be explored and addressed.

Bronchiectasis:

This may be a complicating feature in difficult asthma, either de-novo, in association with fungal disease and atopy (e.g. Allergic Broncho-Pulmonary Aspergillosis), or point to other diagnoses such as ciliary dyskinesia syndromes (e.g. Primary Ciliary Dyskinesia) or Cystic Fibrosis. Always consider the diagnosis of Cystic Fibrosis in the young patient with “apparent asthma” complicated by bronchiectasis, recurrent infections and nasal polyposis. The cornerstone of bronchiectasis management involves regular chest clearance by the patient plus prompt use of antibiotics in an exacerbation.

Obesity:

Obesity is associated with poorly controlled asthma. General measures focussed on weight loss and prevention of deconditioning are central and may improve asthma control.

Obstructive Sleep Apnoea Hypopnoea Syndrome (OSAHS):

OSAHS has been identified as a contributor to frequent exacerbations in patients with difficult asthma. This condition should be looked for in patients with difficult asthma who have high BMI, a thick neck, heavy snoring/ witnessed apnoeas and excessive daytime sleepiness. Weight loss is indicated in all cases. Where associated with significant daytime sleepiness, OSAHS merits specific therapy such as CPAP. In individual cases such treatment has improved asthma control.

Pregnancy:

Asthma control may change in pregnancy and patients should be followed up closely during that period. Poor asthma control in pregnancy can have an adverse effect on the fetus. Conventional asthma medications such as ICS, LABA and theophyllines are not known to convey an increased risk of foetal abnormality and should be continued if already part of the treatment regime. Owing to lack of safety data LTRA should not be commenced in pregnancy. Exacerbations should be treated promptly to avoid foetal hypoxia with oxygen, inhaled or nebulised bronchodilators and systemic corticosteroid as needed.

Occupational-related disease:

An occupational history is essential in adults who develop asthma later in life as up to 20% of adult onset asthma may be due to occupational exposure and the earlier this is identified and the individual removed from that environment the better the long term outcome. Occupational disease would be suggested by worsening of symptoms during periods of work and improvement when away from work, particularly for prolonged periods such as holidays. Knowledge as to whether work involves contact with known respiratory sensitizers aids in the diagnosis and there is classically a period of working in that environment without problems before symptoms start (lag period), which may be many years. Both asthma and rhinitis often co-exist and the onset of the rhinitis may precede the asthma. If occupational asthma is considered the patient should be referred for more formal evaluation.

MARKERS OF POOR OUTCOME:

Certain key characteristics hallmark asthmatic patients at risk of fatal or near-fatal asthma and should always be looked for:

<ul style="list-style-type: none"> ▪ Previous near fatal asthma. (e.g. intubation or respiratory acidosis) ▪ Prior asthma admission in past year. ▪ Need for multiple asthma medications. ▪ Heavy β-agonist use. ▪ Brittle asthma. ▪ Lower social class. ▪ Ethnic minority. ▪ Poor access to healthcare. ▪ Non-compliance. 	<ul style="list-style-type: none"> ▪ Failure to attend appointments. ▪ History of self-discharge. ▪ Social isolation. ▪ Child abuse. ▪ Domestic stress. ▪ Psychological/Psychiatric problems. ▪ Current or recent antipsychotic use. ▪ Denial. ▪ Alcohol or drug abuse. ▪ Obesity. ▪ Employment difficulties. ▪ Financial stress.
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ACUTE EXACERBATIONS

Basic algorithms for the management of acute asthma exacerbations in the Community and within the Hospital setting are outlined on the following pages. Regardless of location, an exacerbation should always prompt an assessment of severity, initiation of appropriate acute therapy and consideration of any need to change long-term therapy. An exacerbation should also always prompt the question, “why has this patient lost asthma control?”

COMMUNITY ACUTE ASTHMA MANAGEMENT GUIDANCE

- Most patients with severe asthma should be treated in hospital
- Mild Exacerbations can be treated in the community

Have a low threshold for admitting patients at high risk of a fatal asthma attack:

- History of intubation and mechanical ventilation for asthma
- Hospitalization in the last year
- History of psychiatric disease
- Currently using or recently stopped treatment with oral glucocorticosteroids

To define severity assess & record:

- Peak flow (PEF)
- Pulse and respiratory rate (RR)
- Oxygen saturations (SaO₂)
- Respiratory examination

SEVERITY

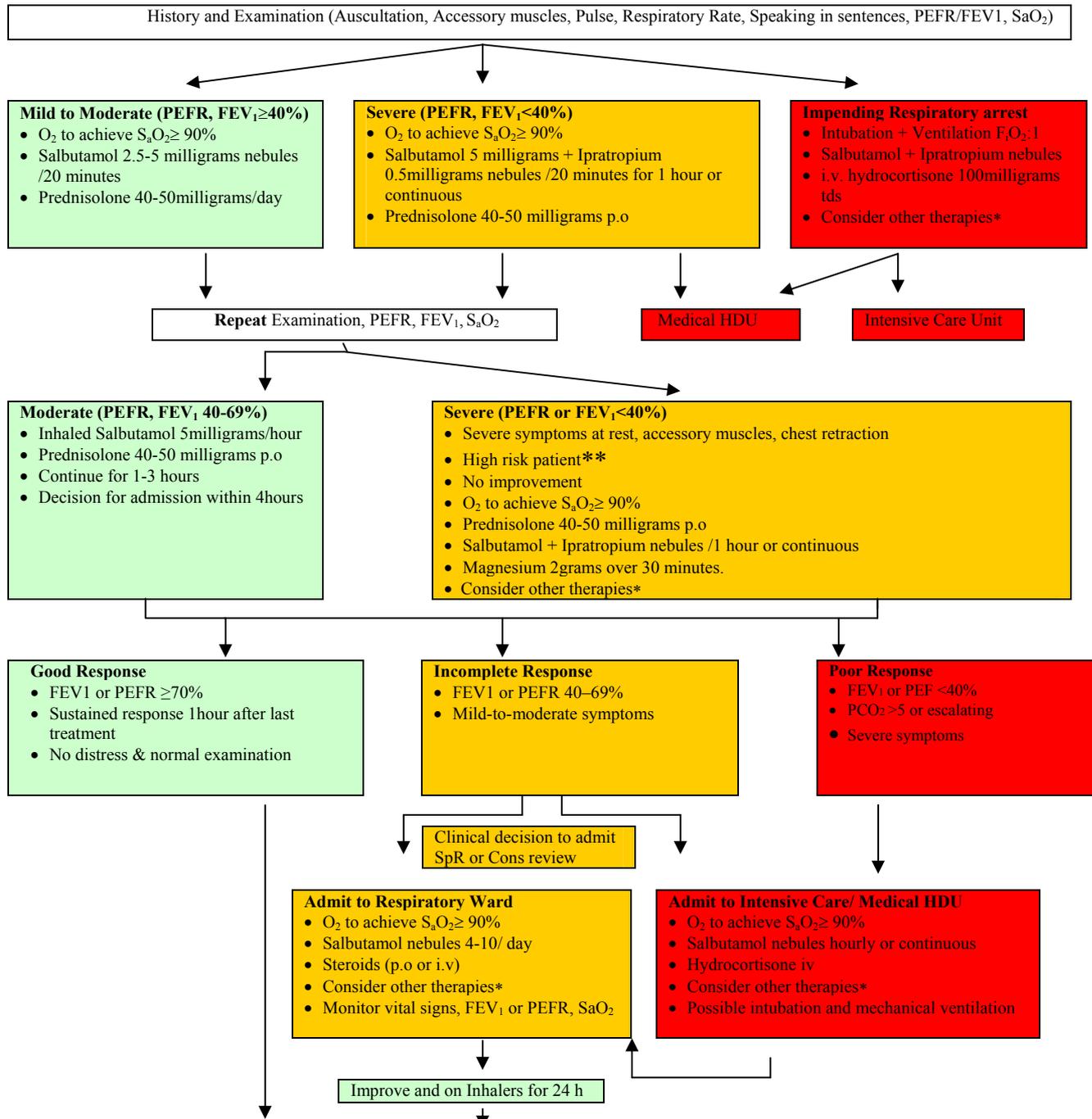
	Mild	Moderate	Severe
The presence of ANY parameter defines severity			
Breathless on	Walking	Talking	Rest
Talks in	Sentences	Phrases	Words
Pulse	<100	100-120	>120 or <60
Resp Rate	<30	<30	>30
PEF	>80% predicted	60-80%	<60%
SaO ₂	>95%	91-95%	<90%

**TREATMENT STRATEGY**

Mild	Moderate	Severe
Treat at home/surgery & assess response to treatment	Consider admission	Admit immediately
<ul style="list-style-type: none"> • Salbutamol 5 milligrams via oxygen driven nebuliser or as high dose inhaler via spacer. • Prednisolone 40 milligrams. • Low threshold for admission if “high risk”. 	<ul style="list-style-type: none"> • Oxygen 40-60%. • Salbutamol 5 milligrams via oxygen driven nebuliser. • Prednisolone 40 milligrams. • Low threshold for admission if “high risk”. 	<ul style="list-style-type: none"> • Oxygen 40-60%. • Salbutamol 5 milligrams & Ipratropium 500 micrograms via oxygen driven nebuliser. • Prednisolone 40 milligrams.
<ul style="list-style-type: none"> • Reassess in 1hr: • Admit if no response to initial treatment. Continue nebuliser in ambulance. • If improving, continue & step up treatment as per action plan. • Complete minimum 7 days of oral steroid. 	<ul style="list-style-type: none"> • Reassess in 1hr: • Admit if no response to initial treatment. Continue nebuliser in ambulance. • If improving, continue & step up treatment as per action plan. • Complete minimum 7 days of oral steroid. 	<p>NOTE: Ensure that all patients with an exacerbation are established on inhaled steroids.</p>

WHY HAS THIS PATIENT LOST ASTHMA CONTROL?

MANAGEMENT OF ASTHMA EXACERBATION IN A+E AND WARDS SOUTHAMPTON UNIVERSITY HOSPITALS TRUST



Discharge:

- Continue inhaled Salbutamol
- Initiate or continue inhaled steroid ± long acting β- agonists
- Continue 5-7 days prednisolone 40-50 milligrams/day p.o
- Patient education (review medications, inhaler technique and environmental control measures; review/initiate action plan)
- Follow up appointment with GP within 48-72 hours

* **MgSO₄**: 2 grams over 30 minutes,
Aminophylline: 5 milligrams/kg over 20 minutes then 0.5 milligrams/kg/hour,
Salbutamol: Start at 300 micrograms/hour then titrate by response within the usual infusion range 3-20 micrograms/minute,
HELIOX: (21% O₂ and 79% He),
Antibiotics: if indicated, **Epinephrine**: 0.3-0.5 milligrams sc at 20 minute intervals for 3 doses. 1:1,000 (1 milligrams/mL),
Montelukast 10 milligrams p.o stat.

** Risk Factors

Asthma history: Previous intubation or ICU, ≥ 2 hospitalisations in the past year, ≥ 3 A+E visits for asthma in the past year, Hospitalisation or A+E visit for asthma in the past month, Using >2 canisters of salbutamol per month, Difficulty perceiving asthma symptoms or severity of exacerbations, lack of a written asthma action plan.

Social history: Illicit drug use, psychosocial problems

Comorbidities: Cardiovascular, other chronic lung disease, chronic psychiatric disease

WRITTEN & SELF MANAGEMENT PLANS

My Asthma **ACTION** Plan

NAME: BEST PEAK FLOW: DATE:

<p>When my asthma is WELL CONTROLLED</p> <ul style="list-style-type: none"> • No regular wheeze, cough or chest tightness by day or night. • Can “work & play” without difficulty. • Need reliever medication less than twice weekly. <ul style="list-style-type: none"> • PEAK FLOW ABOVE 80% OF BEST <div style="border: 1px solid black; width: 100%; height: 15px; margin-top: 5px;"></div>
<p>Continue usual treatment</p>
<p>Preventers:</p> <p>Combination Medication:</p> <p>Reliever:</p>

<p>When my asthma is GETTING WORSE</p> <ul style="list-style-type: none"> • Cough, wheeze or chest tightness by day or night. • Difficulty at work or play because of breathing. • Need reliever medication MORE than twice weekly. <ul style="list-style-type: none"> • PEAK FLOW 50-80% OF BEST <div style="border: 1px solid black; width: 100%; height: 15px; margin-top: 5px;"></div>
<p>Increase treatment</p>
<p><input checked="" type="checkbox"/> I must arrange review with asthma nurse or doctor.</p>

<p>When my asthma is SEVERE</p> <ul style="list-style-type: none"> • Increasing cough, wheeze or chest tightness. • Waking every night and most mornings because of symptoms. • Normal activity difficult because of breathing. • Need reliever medication every 4 hours or more often. • PEAK FLOW LESS THAN 50% OF BEST <div style="border: 1px solid black; width: 100%; height: 15px; margin-top: 5px;"></div>
<p>Increase treatment</p>
<p>! Self-start steroid tablets if kept at home.</p> <p>Consider Emergency Actions.</p> <p><input checked="" type="checkbox"/> I Need urgent medical review.</p>

<p>How to recognise LIFE-THREATENING ASTHMA</p> <p>CALL 999 IF ANY DANGER SIGNS:</p> <ul style="list-style-type: none"> • Extreme difficulty breathing. • Difficulty speaking. • Rapidly worse. • Little relief from medication. • Lips turn blue. <ul style="list-style-type: none"> • PEAK FLOW BELOW 33% OF BEST <div style="border: 1px solid black; width: 100%; height: 15px; margin-top: 5px;"></div>
<p>EMERGENCY ACTIONS</p>
<p>A. Sit upright & stay calm.</p> <p>B. Take 4 separate puffs of a reliever via a spacer (if you have no spacer just use the reliever puffer). Take 5 breaths from the spacer for each puff.</p> <p>C. Wait 5 minutes – if no better take another 4 puffs.</p> <p>D. Keep taking 4 puffs every 5 minutes until help arrives.</p>

MY DOCTOR: MY ASTHMA NURSE: THEIR CONTACT NUMBERS:

MY ASTHMA TRIGGERS ARE:

My Asthma SMART Plan:

NAME: BEST PEAK FLOW: DATE:

When my asthma is WELL CONTROLLED

- No regular wheeze, cough or chest tightness by day or night.
- Can “work & play” without difficulty.
- Need reliever medication less than twice weekly.
- PEAK FLOW ABOVE 80% OF BEST

When my asthma is GETTING WORSE

- IF OVER A PERIOD OF 3 DAYS:
- I am using more than 6 reliever puffs of my SMART inhaler in a day. OR
- I have increasing cough, wheeze or chest tightness by day or night.
- PEAK FLOW 50-80% OF BEST

When my asthma is SEVERE

- IF I NEED MORE THAN 8 EXTRA DOSES OF MY SMART INHALER IN A DAY (MAKING A TOTAL OF 12 PUFFS) THEN I MUST GET MEDICAL HELP THAT DAY!!!!

How to recognise LIFE-THREATENING ASTHMA

CALL 999 IF ANY DANGER SIGNS:

- Extreme difficulty breathing.
- Difficulty speaking.
- Rapidly worse.
- Little relief from medication.
- Lips turn blue.
- PEAK FLOW BELOW 33% OF BEST

Continue usual treatment:

My SMART inhaler is:

Symbicort 100/6 OR Symbicort 200/6

EVERY DAY

Take puffs morning & puffs evening

Always carry my SMART inhaler.

RELIEVER

Use one puff of my SMART inhaler for relief of asthma symptoms

I should:

- Continue to take my regular daily treatment plus an extra puff of my SMART inhaler whenever needed to relieve symptoms.
- Contact my asthma nurse or doctor.
- Start a course of steroid tablets.
- **Must arrange review with asthma nurse or doctor.**

What should I do?

See my asthma nurse, doctor or go to Casualty.

Consider Emergency Actions

EMERGENCY ACTIONS

A. Sit upright & stay calm.

B. Take a puff of my SMART inhaler. If not improving repeat the dose every 10 minutes up to a total of 6 separate doses.

C. If haven't got my SMART inhaler I should use 4 puffs of ventolin via a spacer (if you have no spacer just use the reliever puffer). Take 5 breaths from the spacer for each puff. If no better keep taking 4 puffs every 5 minutes until help arrives.

MY DOCTOR: MY ASTHMA NURSE: THEIR CONTACT NUMBERS:

MY ASTHMA TRIGGERS ARE:

APPENDIX I - THE DRUG COST TABLE (March 2008)

DRUG CLASS	Name	Doses per Device / Container	Cost of Device (£)	Cost of One Month Therapy at Standard Dose (Community) (£)
INHALED SHORT ACTING β -AGONIST	Salbutamol 100 micrograms Easibreathe	200	6.30	
	Salbutamol 100 micrograms mdi	200	1.47	
	Terbutaline 500 micrograms Dry Powder Inhaler (DPI)	100	6.92	
NEBULISED SHORT ACTING β -AGONIST	Salbutamol 2.5 milligrams nebules	20	1.75	
	Salbutamol 5 milligrams nebules	20	2.95	
	Terbutaline 5 milligrams / 2ml nebs	20	4.04	
INHALED LONG ACTING β -AGONIST	Salmeterol 25 micrograms mdi	120	29.26	29.26**
	Salmeterol 50 micrograms accuhaler	60	29.26	29.26*
	Oxis 6 micrograms turbohaler	60	24.80	24.80*
	Oxis 12 micrograms turbohaler	60	24.80	24.80*
	Formoterol 12 micrograms mdi	100	31.28	18.24*
Leukotriene receptor antagonists	Montelukast tablets 10 milligrams	28	26.97	26.97
	Zafirlukast tablets 20 milligrams	56	28.26	28.26
INHALED STEROIDS (Ultrafine CFC-free BDP; Qvar) TWICE potency of other BDP preparations	QVAR 50 micrograms mdi	200	7.87	4.59**
	QVAR 50 micrograms autohaler	200	7.87	4.59**
	QVAR 100 micrograms mdi	200	17.21	10.26**
	QVAR 100 micrograms autohaler	200	17.21	10.26**
INHALED STEROIDS (CFC-free BDP; Clenil Modulite)	Clenil Modulite 50 micrograms mdi	200	3.85	2.30**
	Clenil Modulite 100 micrograms mdi	200	7.72	4.63**
	Clenil Modulite 200 micrograms mdi	200	16.83	10.09**
	Clenil Modulite 250 micrograms mdi	200	16.95	10.16**
INHALED STEROIDS (Budesonide)	Budesonide 50 micrograms mdi	200	7.33	4.34**
	Budesonide 200 micrograms mdi	200	20.90	12.46**
	Budesonide 100 micrograms DPI	200	18.50	11.03**
	Budesonide 400 micrograms DPI	50	18.50	27.73*
INHALED STEROIDS (Fluticasone)	Fluticasone 125 micrograms mdi	120	21.26	21.26**
	Fluticasone 250 micrograms mdi	120	36.14	36.14**
	Fluticasone 250 micrograms accuhaler	60	21.26	21.26*

* Based on one actuation / dose unit twice daily

** Based on two actuations / dose units twice daily

DRUG CLASS	Name	Doses per Device / Container	Cost of Device (£)	Cost of One Month Therapy at Standard Dose (Community) (£)
NEBULISED STEROIDS	Budesonide 500 micrograms /2ml nebs	20	32.00	96.00*
	Budesonide 1milligrams /2ml nebs	20	44.64	133.92*
	Fluticasone 2 milligrams/2ml nebs	10	37.35	224.10*
COMBINATION INHALERS Symbicort – Budesonide + formoterol	Symbicort 100/6 Turbohaler	120	33.00	33.00**
	Symbicort 200/6 Turbohaler	120	38.00	38.00**
	Symbicort 400/12 Turbohaler	60	38.00	38.00*
COMBINATION INHALERS Seretide – Fluticasone and salmeterol	Seretide 50 mdi	120	18.41	18.41**
	Seretide 100 Accuhaler	60	31.19	31.19*
	Seretide 125 mdi	120	36.65	36.65**
	Seretide 250 Accuhaler	60	36.65	36.65*
	Seretide 250 mdi	120	62.29	62.29**
	Seretide 500 Accuhaler	60	40.92	40.92*
COMBINATION INHALERS Beclomethasone + formoterol	Fostair 100/6	120	29.32	29.32**

* Based on one actuation / dose unit twice daily

** Based on two actuations / dose units twice daily

These prices are excluding VAT (17.5%) and are based on the direct acquisition cost of the inhaler device / medicinal product in MIMS March 2008.

APPENDIX II – ALLERGEN AVOIDANCE MEASURES

House Dust Mite:

Several measures can be considered, though their individual clinical efficacy is limited. Selected individuals may derive some benefit from **combinations** of;

1. Encase bedding (mattress, duvet and pillows) in mite-proof covers.
2. Hot wash bed linen (55-60°C).
3. Replace carpets with hard flooring.
4. Use vacuum cleaners with integral HEPA filter and double thickness bags.
5. Hoover the mattress once a fortnight.
6. Damp dusting in the bedroom.
7. Keeping bedroom windows open for a couple of hours a day.

Pets:

Pet allergens are ubiquitous and are seen outside the home in workplaces, schools and on public transport. Several measures can be considered, though their individual clinical efficacy is limited. Selected individuals may derive some benefit from **combinations** of;

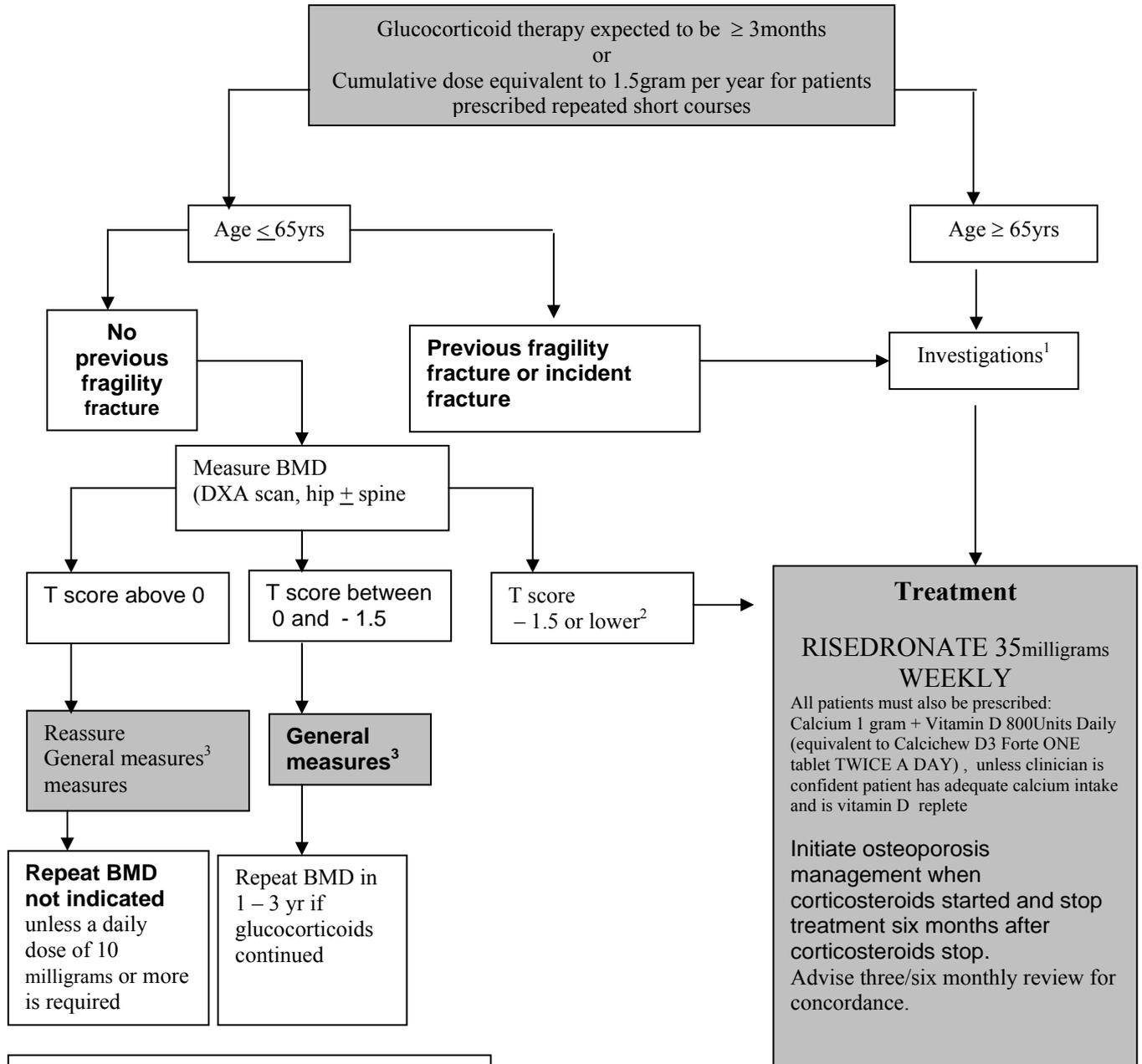
1. Remove pet from the home. Note that even after removal from the home, pet allergen levels may remain elevated for many months. Removal has to be balanced against the potential upset that could result!
2. Keep the pet away from main living areas (e.g. bedrooms).
3. Wash the pet.
4. Replace carpets with hard flooring.
5. Use vacuum cleaners with integral HEPA filter and double thickness bags.

Pollens:

Pollens are impossible to avoid completely. Exposure may be reduced by;

1. Closing doors and windows and remaining indoors when pollen levels are highest (e.g. early mornings and early evenings).
2. Wear sunglasses when pollen levels are high.
3. During the pollen season check the pollen count to guide potential exposure.

APPENDIX III – MANAGEMENT OF STEROID INDUCED OSTEOPOROSIS



- All Patients¹**
- FBC, ESR (If ESR raised, measure serum paraproteins and urine Bence Jones protein)
 - Bone and liver function tests (Ca, P, Alk phos, albumin, ALT/γGT)
 - Serum creatinine
- Additional tests if indicated:
- Serum TSH.
 - Serum 25OH D and PTH
 - Lateral thoracic and lumbar spine X rays
 - Isotope bone scan
 - Serum FSH if hormonal status unclear (women)
 - Serum testosterone, LH and SHBG (men)
 - BMD if monitoring required

- ² Consider treatment depending on age and fracture probability
- General measures³**
- Reduce dose of glucocorticoid when possible,
 - Consider glucocorticoid sparing therapy if appropriate or consider alternative route of administration
 - Recommend good nutrition esp. with adequate calcium and vit D
 - Recommend regular weight bearing exercise
 - Maintain body weight
 - Avoid tobacco use and alcohol abuse (> government recommendations)
 - Assess falls risk and give advice if appropriate

APPENDIX IV - USEFUL CONTACTS

	Department	Contact Name	Telephone Number
SOUTHAMPTON	The Respiratory Centre, Southampton General Hospital (SGH)	Lead Nurse: Sister Katherine Austin Asthma Specialist Nurse: Claire Duffas Lead Physiotherapist: Sarah Ewles Lead Consultants: Dr Ramesh Kurukulaaratchy & Dr Simon Bourne	02380794325
	Medical Pharmacist	Caron Weeks	02380777222 (Bleep #2407)
	Pulmonary Function Testing SGH	John Heath	02380796125
WINCHESTER	Respiratory Consultants	Dr Alan Roberts Dr Alison Grove	
	Respiratory Nurse	Karen Carver	01962825451 (Bleep #143)
	Pulmonary Rehabilitation Nurse	Sarah Symonds	01962825763 (Bleep #049)
	Pulmonary Function Testing	Andrea Douglas-Slater	01962824499
	Respiratory Pharmacist	Kate Newman	01962824833 (Bleep #089)

APPENDIX V - RESOURCES & KEY REFERENCES

Key Learning Resources:

1. **Global Initiative for Asthma. Global strategy for asthma management and prevention. 2006. (www.ginasthma.org)**
2. **ARIA – Allergic Rhinitis and its Impact on Asthma initiative. 2001. (www.whiar.com).**
3. **British guideline on the management of asthma. Thorax 2003; 58 (Suppl I).**
4. **NICE guidance: “Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over”.** *NICE technology appraisal guidance 138* – www.nice.org.uk/TA138. March 2008.
5. **The British Thoracic Society. The burden of lung disease. 2nd edition. 2006.**

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10. Ayres, J. Continuous subcutaneous bronchodilators in brittle asthma. *Brit. J. Hosp. Med*, 1992; 47 (8): 569-71.
11. Humbert M, Beasley R, Ayres J et al. Benefits of Omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60: 309-16.
12. Winchester and Southampton Drugs and Prescribing Committee. Medical management of osteoporosis in adults. August 2007.
13. Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. *Lancet* 2005; 365 (9463): 974-6.
14. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (5 Suppl): S147-334.

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