

Severe asthma – A pragmatic guide for primary care practitioners



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This pragmatic guide on the identification, referral and ongoing management of adults and children with severe asthma has been developed by an expert group led by Dr Steve Holmes, a GP based in Shepton Mallet, Somerset and including Will Carroll, University Hospital of the North Midlands, Stoke-on-Trent, Fiona Mosgrove, Clinical Lead Grampian Respiratory Improvement Programme, Angela Pugh of the University Hospital of Llandough Cardiff & Vale University Health Board and Robert Stone, Taunton and Somerset NHS Foundation Trust.



Key facts:

- Asthma UK suggest that there are an estimated 5.4 million individuals living with asthma in the UK.¹
- Around 5% of people with asthma have severe asthma.² This equates to around 200,000 people in the UK.¹
- Only around 18% of people with asthma who would benefit from specialist asthma care receive the appropriate referral.³
- It is estimated that ~50,000 patients with severe asthma may be eligible for biologic therapy, although currently <10,000 are receiving such therapy.⁴



Introduction

Asthma is a chronic respiratory disease that is estimated to affect around 5.4 million people in the UK.¹ The severity of asthma symptoms can fluctuate over time and in response to specific triggers which can precipitate acute exacerbations, which can be described as moderate, severe or life-threatening.⁵ Patients with asthma require ongoing monitoring and management to identify triggers and ensure optimal control of symptoms on a day to day basis.^{5,6} Inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA) are the mainstay of treatment along with short-acting bronchodilators for as-needed, short-term use.^{5,6}

A proportion of patients, however, will continue to experience daily symptoms and acute exacerbations despite the prescription of standard asthma medications. This may be due to poor adherence to therapy, poor inhaler technique or a requirement for an increased dose of medication. For a small number of patients, the reasons for apparent poor control may be because their asthma is driven by airways inflammation that is less responsive to standard inhaled corticosteroid therapy – these patients



are described as having severe asthma and are the most difficult to treat group of patients with asthma.^{1,7}

An estimated 4 out of every 100 people with asthma are living with severe asthma. In the UK, this equates to around 200,000 people.¹ Patients with severe asthma are at the highest risk for severe, life-threatening asthma exacerbations and often live with debilitating daily symptoms as well as the consequences of frequent courses of oral steroids used to treat their condition. These patients require referral for specialist review in a severe asthma service where options for further treatments can be assessed including biologic therapy, bronchial thermoplasty or immunosuppressant therapy.⁸

In 2020, the Primary Care Respiratory Society (PCRS) published a pragmatic guide for primary care to support the identification, review and, where appropriate, referral of patients with poorly controlled asthma.⁸ Since then several biologic agents for the treatment of patients with certain subtypes of

severe asthma have been approved for use in the UK. Here we provide an updated pragmatic guide to reflect novel tools, initiatives and pathways of care for people with severe asthma to ensure they are identified and referred for specialist review and, where appropriate, have access to biologic therapy.

Severe asthma

Severe asthma is caused by uncontrolled airways inflammation due to the persistent activation of specific inflammatory pathways. The British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) use measures of asthma control to define asthma severity. Individuals with more than two asthma attacks a year or persistent symptoms with short-acting beta-2-agonist (SABA) use more than twice a week despite specialist-level therapy of asthma and comorbidities have severe asthma (Table 1).⁵ The ERS/ATS joint guidelines define asthma severity based upon the treatment required. Severe asthma

Table 1. Definition of asthma exacerbations⁵

Definition of asthma exacerbations in adults	Definition of asthma exacerbation in children and young people
<p>Moderate acute</p> <ul style="list-style-type: none"> Increasing symptoms PEF >50–75% best or predicted No features of acute severe asthma 	<p>Moderate acute</p> <ul style="list-style-type: none"> Able to talk in sentences SpO₂ ≥92% PEF ≥50% best or predicted Heart rate <ul style="list-style-type: none"> ≤140 bpm in children aged 1–5 yrs ≤125 bpm in children 5 yrs Respiratory rate <ul style="list-style-type: none"> ≤40/min in children aged 1–5 yrs ≤30/min in children 5 yrs
<p>Acute severe</p> <p>Any of:</p> <ul style="list-style-type: none"> PEF 33–50% best or predicted Respiratory rate ≥25/min Heart rate ≥110 bpm Inability to complete sentences in one breath 	<p>Acute severe</p> <ul style="list-style-type: none"> Cannot complete sentences in one breath or too breathless to talk or feed SpO₂ <92% PEF ≥50% best or predicted Heart rate <ul style="list-style-type: none"> >140 bpm in children aged 1–5 yrs >125 bpm in children 5 yrs Respiratory rate <ul style="list-style-type: none"> >40/min in children aged 1–5 yrs >30/min in children 5 yrs
<p>Life threatening</p> <p>Any one of the following in a patient with severe asthma:</p> <ul style="list-style-type: none"> Clinical signs: altered conscious level, exhaustion, arrhythmia, hypotension, cyanosis, silent chest, poor respiratory effort Measurements: PEF <33% best or predicted, SpO₂ <92%, PaO₂ <8 kPa, 'normal' PaCO₂ (4.6–6.0 kPa) 	<p>Life threatening</p> <p>Any one of the following in a patient with severe asthma:</p> <ul style="list-style-type: none"> Clinical signs: exhaustion, hypotension, cyanosis, silent chest, poor respiratory effort, confusion Measurements: PEF <33% best or predicted, SpO₂ <92%
<p>Near-fatal</p> <ul style="list-style-type: none"> Raised PaCO₂ and/or requiring mechanical ventilation with raised inflation pressures 	

bpm, beats per minute; PaCO₂, partial pressure of CO₂; PaO₂, partial pressure of oxygen; PEF, peak expiratory flow; SpO₂, oxygen saturation; yrs, years.

requires medications suggested for Global Initiative for Asthma (GINA) steps 4 and 5 (high dose ICS + LABA or leukotriene receptor antagonist [LTRA] or theophylline) for the previous year or systemic corticosteroids for at least 6 of the previous 12 months to prevent asthma becoming uncontrolled, or which remains uncontrolled despite this therapy.⁹

Patients with a current diagnosis of severe asthma are estimated to account for around 5% of all asthma patients, equating to around 200,000 individuals in the UK.^{2,10}

Proactive identification of patients with poor asthma control

Proactive identification of patients with poor asthma control is essential to optimise treatment and reveal the subset of patients with severe asthma.

A search of the primary care practice database can be used to identify patients for urgent review. For example, a history of asthma exacerbations: patients requiring two or more courses of oral corticosteroids (OCS) for asthma exacerbations in the previous 12 months should be referred for secondary care review. SABA use/prescribing and hospital admission frequencies are other metrics that can be used to identify patients with poor asthma control including those with severe asthma. Patients with severe asthma are likely to be experiencing daily symptoms, their symptom burden may have become normalised for them and they might consider that they are managing those symptoms effectively with what is in fact overuse of their rescue SABA therapy.¹¹ There are currently no formal guidelines on which to define a threshold for rescue SABA overuse based on prescription frequency. PCRS suggest that the prescription of three or more SABA canisters in a 12-month period may indicate SABA over-reliance and prompt an urgent review with a view to referral for secondary care review. In Wales, guidelines suggest that adults requesting 6 or more SABA canisters a year require an urgent review and patients collecting fewer than 12 preventer inhalers each year (assuming a 1 month supply per prescribed inhaler) should be highlighted for review.¹² The National Bundle of Care for Children and Young People with Asthma advises that all children and young people who have been prescribed more than 3 short-acting reliever inhalers in the previous 12 months are invited for an urgent review of their asthma control.⁴

Asthma Right Care (ARC) is a global initiative developed by the International Primary Care Respiratory Group (IPCRG) and launched in the UK by PCRS in 2019 that aims to enable identification of patient using levels of SABA that might indicate poor asthma control (<https://www.pcrs-uk.org/resource/asthma-right-care>). Identifying such patient and understanding and addressing

underlying reasons for SABA overuse such as poor adherence to their maintenance medication is a valuable approach to both improve asthma care and identify the subset of patients who may require specialist evaluation.

Box 1: How to access Asthma Right Care educational resources and practical tools.

To access the Asthma Right Care suite of resources and tools visit the PCRS website at <https://www.pcrs-uk.org/resource/asthma-right-care>

Resources available open access include:

- An article describing the nine good asthma care processes.
- Practice and pharmacy posters highlighting the benefit of regular preventer inhaler therapy.
- A set of playing cards to trigger conversations with healthcare teams, and between pharmacists and patients regarding the use of/reliance on SABA inhalers.
- An article describing the building blocks of a good asthma review in adults.

The NHS Accelerated Access Collaborative (AAC) identified access to biologic agents for patients with severe asthma as a key target for their Rapid Uptake of Products (RUP) programme.⁴ AAC have worked with a number of organisations to develop tools to facilitate the identification of patients with severe asthma who may require biologic therapies as part of their package of care. One such tool is the SPECTRA Primary Care Clinical System resource, developed in collaboration with AstraZeneca to facilitate the search of practice databases to identify patients with risk factors that may indicate severe asthma. These patients can then be invited for an asthma review by their primary care team.

Box 2: How to access the SPECTRA Clinical System resources

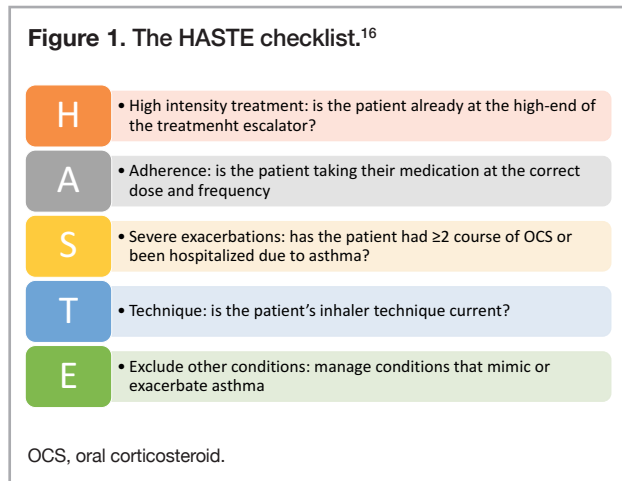
To access clinical system resources and reporting you can register via the website at www.suspected-severe-asthma.co.uk.

Additional information and support is available:
Telephone: 01332 546 909
Email: support@suspected-severe-asthma.co.uk

When to suspect severe asthma

The role of primary care is to identify those patients whose asthma is not well controlled and understand the reasons for their poor symptom control. Poor asthma control may be due to poor adherence to their current prescribed regimen, incorrect inhaler technique resulting in under-dosing of their prescribed medi-

cation, exposure to avoidable triggers, smoking (or exposure to second-hand tobacco smoke) or the effects of co-morbid conditions which can be optimised with current treatments. The HASTE tool provides an aide memoire for healthcare professionals undertaking asthma reviews to collate the key information that may indicate a referral for specialist evaluation is appropriate (Figure 1).



A diagnosis of severe asthma may be considered when asthma control is not achieved despite:

- Confirmation of the asthma diagnosis.
- Optimisation of asthma medication including dose of ICS and, as appropriate, addition of long acting bronchodilators, LTRAs or theophylline.
 - o Consideration of maintenance and reliever therapy (MART) with appropriate ICS-formoterol inhalers.
- A review and coaching of inhaler technique.
- A review of their exposure to known and emergent triggers.
- A review of their general health to identify any comorbid conditions or aggravating problems such as smoking.

A reasonable timeframe to attempt optimisation of treatment would be 6 months.¹³ Table 2 provides an algorithm for the identification, referral and ongoing care of patients with severe asthma, highlighting the red flags indicating severe asthma requiring referral for specialist evaluation.

Pathways of care for patients with severe asthma

When severe asthma is suspected the patient should be referred for secondary care specialist review. In 2021, recommendations were made to improve referral process from primary to specialist care.¹⁴ These include the direct referral of patients with suspected severe asthma to a severe asthma network (or service) by both primary and secondary care teams.

NHS England and NHS Improvement recommend that all

adults newly diagnosed with severe asthma should receive a multidisciplinary team (MDT) review of their care by a specialist asthma MDT hosted by a designated severe asthma specialist centre.² Although Wales does not have a commissioning service for asthma, the All Wales Prescribing Advisory Group (AWPAG) recommended that the severe asthma specialist teams can assess the suitability of patients for biological medicines including making use of the All Wales Severe Asthma multidisciplinary team. Similar pathways are yet to be established in Scotland and Northern Ireland. The situation is less clear for children and young people. Currently, severe asthma services for children are not formally commissioned and details are lacking of the specific requirements of a specialist difficult asthma service. Therefore, the severe asthma service provided for children and young people by specialist respiratory centres varies between providers. Referral for tertiary level specialist opinion should be considered if, despite secondary care specialist review, the patient and clinician agree that clinical improvement does not match their expectations.

Box 3: An example of a digital tool to support specialist referral decision making

One tool to support specialist referral decision making is the Asthma Referral Identifier. This is a referral decision tool developed by panel of experts in the field of asthma care in collaboration with AstraZeneca and is based on GINA Global Strategy for Asthma Management Prevention 2020. The Asthma Referral Identifier is available via GP Notebook (<https://gpnotebook.com/en-gb/asthma-refer-id/index.cfm>) and uses medication history, history of exacerbations, hospitalizations and ICU care and SABA use in the previous 12 months to generate a summary report and, for patients who might benefit from an asthma review by a specialist clinician, generates a referral letter.

Treatment of the patient with severe asthma

Biologic agents are prescribed in tertiary and some secondary care settings by specialist severe asthma multi-disciplinary teams.⁴ In England, it is estimated that ~50,000 patients with severe asthma may be eligible for biologic therapy, although prescribing data suggests between 8,000 and 10,000 patients are currently receiving such therapy.^{4,15} These agents specifically target the inflammatory pathways that drive the pathogenesis of severe asthma, reducing symptoms and exacerbations and they reduce the need for oral steroids. Biologics approved for the treatment of severe asthma in the UK include omalizumab and mepolizumab from the age of 6 years, dupilumab from the age

Table 2. Algorithm for the identification, referral and ongoing care of patients with severe asthma.

Element	Actions and responsibilities	Useful resources/tools		
Identification of patient with possible/suspected severe asthma:	<ul style="list-style-type: none"> • Via annual review • Via practice database search • Via follow-up after an exacerbation 	SPECTRA Clinical System resources: To access clinical system resources and reporting you can register via the website at www.suspected-severe-asthma.co.uk .		
5-step primary care review: <i>Recommended maximum time to attempting optimisation: 6 months (Oxford Academic Health Science Network, April 2022)</i>	<ol style="list-style-type: none"> 1. Confirm asthma diagnosis 2. Review and optimise asthma medication 3. Review inhaler technique and coach as appropriate 4. Review exposures, including smoking and second-hand tobacco smoke exposure 5. Review general health and comorbid conditions (known and emergent) 	Asthma Right Care educational resources and practical tools. To access the Asthma Right Care suite of resources and tools visit the PCRS website at https://www.pcrs-uk.org/resource/asthma-right-care		
Red flags indicating need for referral for specialist evaluation:	<p>Any of the following despite confirmation of asthma diagnosis and optimisation of standard management:</p> <ul style="list-style-type: none"> ▶ Two or more courses of oral corticosteroids over the past 12 months ▶ Two or more emergency attendances, admission or unscheduled hospital visit due to asthma over the past 12 months ▶ History of intubation or admission to an intensive care unit or high dependency unit due to asthma ▶ Three or more SABA inhalers prescribed and confirmed as used in the last 12 months 	<p>HASTE tool: https://www.oxfordahsn.org/wp-content/uploads/2022/05/AB-podcast-poster.pdf</p> <p>SPECTRA Clinical System resources To access clinical system resources and reporting you can register via the website at www.suspected-severe-asthma.co.uk.</p>		
Referral to secondary/tertiary care:	<p>Referral should include clinical findings supporting a suspicion for severe asthma and confirmation and associated findings from the 5-step primary care review.</p> <p>Referral letter to include:</p> <ul style="list-style-type: none"> • Reason for referral • Current asthma treatment and previously tried treatment • Number of courses of steroids (for asthma) in previous 12 months • Number of emergency department and hospital admission for asthma in previous 12 months • Number of ICS-containing inhalers prescribed in previous 12 months • Any relevant comorbidities • Results of relevant investigations (e.g. spirometry, PEFr monitoring, blood eosinophil count, FeNO, total IgE) • Smoking history and BMI 	Asthma Referral Identifier available via GP Notebook: https://gpnotebook.com/en-gb/asthma-refer-id/index.cfm		
Ongoing management responsibilities:	<table border="0"> <tr> <td> <p>Primary care team:</p> <ul style="list-style-type: none"> • Annual asthma review • Ensure SNOMED code for severe asthma is applied (once severe asthma diagnosed) </td> <td> <p>Specialist care team:</p> <ul style="list-style-type: none"> • Prescribing biologics • Monitoring response to biologic treatment (annual review) • Training on self-administration of medication where appropriate • Obtaining consent and registering patients with the UK Severe Asthma Registry </td> </tr> </table>	<p>Primary care team:</p> <ul style="list-style-type: none"> • Annual asthma review • Ensure SNOMED code for severe asthma is applied (once severe asthma diagnosed) 	<p>Specialist care team:</p> <ul style="list-style-type: none"> • Prescribing biologics • Monitoring response to biologic treatment (annual review) • Training on self-administration of medication where appropriate • Obtaining consent and registering patients with the UK Severe Asthma Registry 	AAC Consensus Pathway: Management of Uncontrolled Asthma in Adults, April 2022. Available at: www.oxfordahsn.org
<p>Primary care team:</p> <ul style="list-style-type: none"> • Annual asthma review • Ensure SNOMED code for severe asthma is applied (once severe asthma diagnosed) 	<p>Specialist care team:</p> <ul style="list-style-type: none"> • Prescribing biologics • Monitoring response to biologic treatment (annual review) • Training on self-administration of medication where appropriate • Obtaining consent and registering patients with the UK Severe Asthma Registry 			

AAC, Accelerated Access Collaborative; BMI, body mass index; ICS, inhaled corticosteroid; PEFr, peak expiratory flow rate; SABA, short-acting bronchodilator.

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of 12 years and reslizumab and benralizumab in adults (Table 3). They are given regularly either in hospital as an injection or infusion or at home self-injected by patients.

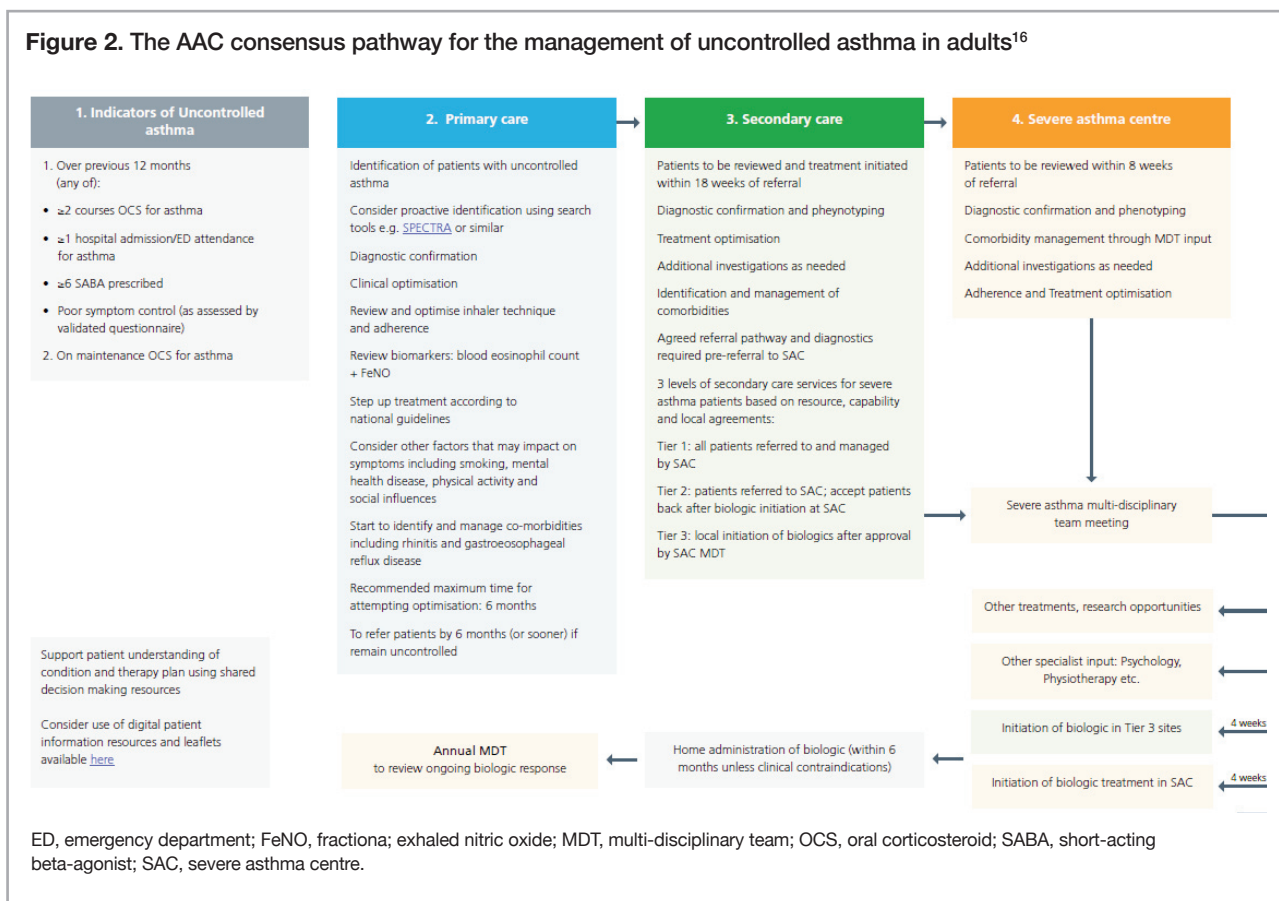
For those patients not eligible for biologic therapy, a proportion will benefit from specialist intervention to optimise their standard medication regimen, address specific comorbidities or

Table 3. Biologics approved for the treatment of severe asthma in the UK (correct as of December 2022).

Biologic agent	Mechanism of action	Indication	Dose and administration	Eligibility criteria ^a	Most common adverse events
Omalizumab ¹⁷	Binds to IgE thereby inhibiting IgE-mediated inflammation	For adults and children ≥ 6 years of age with moderate to severe persistent asthma whose asthma symptoms are not well controlled with asthma medicines called inhaled corticosteroids	Subcutaneous Every 2 week or every week (base on IgE and weight)	IgE-mediated asthma Continuous or frequent OCS (≥ 4 courses in the previous 12 months)	Headache and injection site reactions (pain, swelling, erythema, pruritus)
Mepolizumab ¹⁸	Inhibits IL-5, a cytokine responsible for the growth, differentiation and activation of eosinophils, thereby reducing the production and survival of eosinophils	For adults and children ≥ 6 years of age with severe eosinophilic asthma	Subcutaneous Every 4 weeks	If eosinophils ≥ 300 cells/ μ L: • ≥ 4 exacerbations in previous 12 months OR continuous OCS If eosinophils ≥ 400 cells/ μ L: • ≥ 3 exacerbations in previous 12 months needing systemic CS	Headache, injection site reactions (pain, swelling, erythema, pruritus) and back pain
Benralizumab ¹⁹	Inhibits IL-5, a cytokine responsible for the growth, differentiation and activation of eosinophils, thereby reducing the production and survival of eosinophils	For adults with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA	Subcutaneous Every 4 weeks for the first 3 doses, then every 8 weeks	If eosinophils ≥ 300 cells/ μ L: • ≥ 4 exacerbations in previous 12 months OR continuous OCS If eosinophils ≥ 400 cells/ μ L: • ≥ 3 exacerbations in previous 12 months needing systemic CS	Headache and pharyngitis
Reslizumab ²⁰	Inhibits IL-5, a cytokine responsible for the growth, differentiation and activation of eosinophils, thereby reducing the production and survival of eosinophils	Adults with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment	Intravenous 3 mg/kg every 4 weeks	Eosinophils ≥ 400 cells/ μ L ≥ 3 exacerbations in previous 12 months needing systemic CS	Increased blood creatine phosphokinase and anaphylactic reaction
Dupilumab ²¹	Inhibits IL-4 through the Type 1 IL-4 receptor and IL-4 and IL-13 signaling through the respective Type 2 receptors	Adults and adolescents (≥ 12 years) with severe asthma with type 2 inflammation who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment	Subcutaneous Every 2 weeks	Type 2 inflammation-associated asthma Raised blood eosinophils (≥ 150 cells/ μ L), raised FeNO and ≥ 4 exacerbations in the last 12 months Ineligible for mepolizumab, reslizumab or beralizumab or has not responded to these agents	Injection site reactions, conjunctivitis, arthralgia, oral herpes and eosinophilia

^a NICE Technology appraisal guidance: Omalizumab, <https://www.nice.org.uk/guidance/ta278/chapter/1-Guidance>; mepolizumab, <https://www.nice.org.uk/guidance/TA671/chapter/1-Recommendations>; benralizumab, <https://www.nice.org.uk/guidance/TA565/chapter/1-Recommendations>; reslizumab, <https://www.nice.org.uk/guidance/TA479/chapter/1-Recommendations>; dupilumab, <https://www.nice.org.uk/guidance/TA751/chapter/1-Recommendations>.
FeNO, fractionated nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta-agonist; OCS, oral corticosteroid.

Figure 2. The AAC consensus pathway for the management of uncontrolled asthma in adults¹⁶



issues around adherence that may prevent optimal control. A small proportion of patients will remain poorly controlled and ineligible for biologic therapy with few alternative treatment options at this time. It is essential that these patients are identified and monitored by specialist asthma care teams in collaboration with primary care colleagues and continue to receive annual asthma reviews with their primary care providers.

Monitoring and follow-up of the patient with severe asthma

All patients with asthma should receive an annual asthma review with their primary care team.⁶ Patients with severe asthma receiving biologic therapy will remain under specialist care where their response to treatment will be monitored and treatment adjusted as required to achieve optimal symptoms control. Patients with confirmed severe asthma receiving shared care (primary and secondary care) or referred back to primary care for ongoing management, may require more frequent review and additional support from their primary care team. Patients receiving biologic therapy will have direct access to and regular review by their secondary care team. These patients should also continue to receive their annual asthma review with the primary care

team to monitor patients from a holistic perspective, monitor prescription refills and address mental health and psychological well-being issues that may not be captured during secondary care consultations.

The AAC Consensus Pathway for the management of adults with uncontrolled asthma published in June 2022 recommends that local health care systems should consider implementing an integrated care model with the formation of a respiratory MDT that includes a Respiratory Consultant, specialist nurse, practice nurse, GP, district nurse and pharmacist (Figure 2).¹⁶ This approach would ensure a personalised model of care enabling diagnostic clarification, complex patient discussions and identification of patients with potential severe asthma earlier.

Pragmatic Guidance

See overleaf.

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A proactive approach should be taken to the identification of patients with potential severe asthma.

- ▶ Consider a proactive search of your clinical practice database to identify patients with markers of poor asthma control for urgent review. Example metrics include:
 - ▶ Three or more SABA inhalers prescribed and confirmed as used in the last 12 months
 - ▶ Fewer than 12 preventer canisters collected in the last 12 months (assuming each canister is 1 months' supply)
- ▶ Consider using an aide memoire such as the HASTE tool to quickly review and identify patients who might benefit from specialist referral and evaluation.

Take a 5-step approach to the review of patients identified with uncontrolled asthma. If no improvement is observed despite optimised treatment, refer for specialist care.

1. Confirm asthma diagnosis and consider objective measures of (i) asthma control (e.g ACT or ACQ6 questionnaires) or evaluation of markers of Type 2 inflammation (e.g elevated eosinophils or IgE)
2. Review and optimise asthma medication
3. Review inhaler technique and coach as appropriate
4. Review exposures, including smoking and second-hand tobacco smoke exposure
5. Review general health and comorbid conditions (known and emergent)

A patient with potential severe asthma should be referred for specialist review when:

- ▶ Two or more courses of oral corticosteroids over the past 12 months
- ▶ Two or more emergency attendances, admissions or unscheduled hospital visits due to asthma over the past 12 months
- ▶ History of intubation or admission to an intensive care unit or high dependency unit due to asthma

Identify how the Severe Asthma Service operates in your locality. Asthma services are increasingly being networked with respiratory teams working collegiately to deliver uniform care across geographic regions using a hub and spoke model.

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