GINA Pocket Guide
Difficult to treat and severe asthma in adults and adolescents

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Current severe asthma guidelines – 2014 and 2020

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

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Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline

Chung et al, ERJ 2014

Holguin et al, ERJ 2020
About the GINA strategy

- The GINA report is not a guideline, but an integrated evidence-based strategy focusing on translation into clinical practice.

- Recommendations are framed, not as answers to isolated PICOT questions, but as part of an integrated strategy, in relation to:
  - The GINA goals of preventing asthma deaths and exacerbations, as well as improving symptom control.
  - Current understanding of underlying disease processes.
  - Human behavior (of health professionals and patients/carers).
  - Implementation in clinical practice.
  - Global variation in populations, health systems and medication access.

- GINA provides practical resources for clinicians:
  - Figures and tables about implementation in clinical practice: not just ‘what’, but ‘how to’.
  - This pocket guide was developed in response to feedback from GINA Assembly members that strongly encouraged development of a practical resource about severe asthma.
Goals of asthma treatment

- Few asthma symptoms
- No sleep disturbance
- No exercise limitation
- Maintain normal lung function
- Prevent flare-ups (exacerbations)
- Prevent asthma deaths
- Avoid medication side-effects

Symptom control

Risk reduction

- The patient’s goals may be different from these
- Symptoms and risk may be discordant – need to assess both
Terminology

- **Uncontrolled asthma**
  - Frequent symptoms and/or flare-ups (exacerbations)
  - Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly

- **Difficult-to-treat asthma**
  - (not difficult patients!)
  - Asthma uncontrolled despite prescribing medium or high dose preventer treatment
  - Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities

- **Severe asthma**
  - “Severe asthma” has had many different meanings \((Taylor, ERJ 2008; Reddel AJRCCM 2009)\)
  - Now defined as asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased \((Chung, ERJ 2014)\)
    - i.e. relatively refractory to corticosteroids (rarely completely refractory)
  - A retrospective definition, dependent on how thoroughly contributory factors are excluded
Phenotype: The observable characteristics of a disease, such as morphology, development, biochemical or physiological properties, or behaviour.

- Patients with an identified phenotype of obstructive lung disease may share a cluster of clinical, functional and/or inflammatory features, without any implication of a common underlying mechanism
- Examples: allergic asthma, aspirin-exacerbated respiratory disease, severe eosinophilic asthma

Endotype: A subtype of disease, defined functionally and pathologically by a distinct molecular mechanism or by distinct treatment responses (Anderson, Lancet 2008)

- Among patients with obstructive lung disease, there are likely to be several specific endotypes associated with divergent underlying molecular causes, and with distinct treatment responses. These endotypes may or may not align with clinical or inflammatory phenotypes identified from studies limited to asthma or to COPD
- Examples: emphysema due to alpha1-antitrypsin deficiency

Biomarker: A defined characteristic measured as an indicator of normal biologic processes, pathogenic processes or response to an intervention

- Potential examples: FeNO, blood eosinophils – but these may not meet quality criteria for biomarkers
What proportion of adults with asthma have severe asthma?

24%

High intensity treatment
= high dose ICS-LABA
or medium dose
ICS-LABA + OCS)

Based on data from Hekking et al, JACI 2015
What proportion of adults with asthma have severe asthma?

24% High intensity treatment
= high dose ICS-LABA or medium dose ICS-LABA + OCS

17% difficult-to-treat asthma
= high intensity treatment + poor symptom control

Based on data from Hekking et al, JACI 2015
What proportion of adults with asthma have severe asthma?

Based on data from Hekking et al, JACI 2015
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## Investigate and manage adult and adolescent patients with difficult-to-treat asthma

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## Assess and treat severe asthma phenotypes

**SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE**

- 5 Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations .......................... 10 ...... 20
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## Monitor / Manage severe asthma treatment

**SPECIALIST AND PRIMARY CARE IN COLLABORATION**

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GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

1. Confirm the diagnosis (asthma/differential diagnoses)
2. Consider referring to specialist or severe asthma clinic at any stage
3. Optimize management, including:
4. Review response after ~3-6 months

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SPECIALIST CARE: SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

5. Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations

6a. Consider non-biologic treatments
Assess and treat severe asthma phenotypes cont'd

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider **add-on biologic Type 2** targeted treatments
Monitor / Manage severe asthma treatment

7 Review response

8 Continue to optimize management
Severe asthma decision tree: diagnosis and management

GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

Key
- decision, filters
- intervention, treatment
- diagnosis, confirmation
Severe asthma decision tree: diagnosis and management

GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

1. **Confirm the diagnosis** (asthma/differential diagnoses)

   For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

2. **Look for factors** contributing to symptoms, exacerbations and poor quality of life:
   - Incorrect inhaler technique
   - Suboptimal adherence
   - Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
   - Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE), medications such as beta-blockers and NSAIDs
   - Overuse of SABA relievers
   - Medication side effects
   - Anxiety, depression and social difficulties

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**Key**
- decision, filters
- intervention, treatment
- diagnosis, confirmation
Severe asthma decision tree: diagnosis and management

GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS:
"Difficult-to-treat asthma"

1. Confirm the diagnosis (asthma/differential diagnoses)

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

2. Look for factors contributing to symptoms, exacerbations and poor quality of life:
   - Incorrect inhaler technique
   - Suboptimal adherence
   - Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
   - Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE), medications such as beta-blockers and NSAIDs
   - Overuse of SABA relievers
   - Medication side effects
   - Anxiety, depression and social difficulties

3. Optimize management, including:
   - Asthma education
   - Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
   - Treat comorbidities and modifiable risk factors
   - Consider non-biologic add-on therapy (e.g. LABA, LAMA, LMTTRA, if not used)
   - Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
   - Consider trial of high dose ICS-LABA, if not used

Key
- decision, filters
- intervention, treatment
- diagnosis, confirmation
Severe asthma decision tree: diagnosis and management

**GP OR SPECIALIST CARE**

**Investigate and manage adult and adolescent patients with difficult-to-treat asthma**

- **1. Confirm the diagnosis** (asthma/differential diagnoses)
- **2. Look for factors** contributing to symptoms, exacerbations and poor quality of life:
  - Incorrect inhaler technique
  - Suboptimal adherence
  - Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
  - Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE), medications such as beta-blockers and NSAIDs
  - Overuse of SABA relievers
  - Medication side effects
  - Anxiety, depression and social difficulties

- **3. Optimize management**, including:
  - Asthma education
  - Optimize treatment (e.g., check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
  - Treat comorbidities and modifiable risk factors
  - Consider non-biologic add-on therapy (e.g., LABA, LAMA, LMI/LTRA, if not used)
  - Consider non-pharmacological interventions (e.g., smoking cessation, exercise, weight loss, mucous clearance, influenza vaccination)
  - Consider trial of high dose ICS-LABA, if not used

- **4. Review response after ~3-6 months**

**Key**
- decision, filters
- intervention, treatment
- diagnosis, confirmation

**Diagnosis:** "Severe asthma"
- If not done by now, refer to a specialist, if possible.

**Is asthma still uncontrolled?**
- yes
  - Consider stepping down treatment, OCS first (if used.)
- no
  - Continue optimizing management

**Does asthma become uncontrolled when treatment is stepped down?**
- yes
  - Restore previous dose
- no

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS
Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

5. Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations

6a. Consider non-biologic treatments

Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)

**Type 2 inflammation**

- Could patient have Type 2 airway inflammation?
  - Blood eosinophils ≥150/µl and/or
  - FeNO ≥20 ppb and/or
  - Sputum eosinophils ≥2%, and/or
  - Asthma is clinically allergen-driven and/or
  - Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

Note: these are not the criteria for add-on biologic therapy (see 6b)

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest, DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion

- Consider need for social/psychological support

- Involve multidisciplinary team care (if available)

- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)
Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

5. Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations

6a. Consider non-biologic treatments

Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)

Type 2 inflammation

- Could patient have Type 2 airway inflammation?
  - Blood eosinophils ≥150/μl and/or
  - FeNO ≥20 ppb and/or
  - Sputum eosinophils ≥2%, and/or
  - Asthma is clinically allergen-driven and/or
  - Need for maintenance OCS
  (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of LAMA or azithromycin (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

Investigate for comorbidities/differential diagnoses and treat/refer as appropriate

- Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest, DlCO
- Skin prick testing or specific IgE for relevant allergens, if not already done
- Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion

Consider need for social/psychological support

Involves multidisciplinary team care (if available)

Invite patient to enroll in registry (if available) or clinical trial (if appropriate)
Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

5. Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations

6a. Consider non-biologic treatments

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)

Type 2 inflammation

- Could patient have Type 2 airway inflammation?
- Yes: 
  - Blood eosinophils ≥150 μl and/or
  - FeNO ≥20 ppb and/or
  - Sputum eosinophils ≥2%, and/or
  - Asthma is clinically allergen-driven and/or
  - Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

- No:
  - Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
    - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins, CXR and/or HRCT chest, DLCO
    - Skin prick testing or specific IgE for relevant allergens, if not already done
    - Other directed testing (e.g., ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
  - Consider need for social/psychological support
  - Involve multidisciplinary team care (if available)
  - Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of LAMA or azithromycin (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
  - Consider bronchial thermoplasty (+ registry)
Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

5. Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations

6a. Consider non-biologic treatments

Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)

Type 2 inflammation

- Could patient have Type 2 airway inflammation?
  - Blood eosinophils ≥150/µl and/or
  - FeNO ≥20 ppb and/or
  - Sputum eosinophils ≥2%, and/or
  - Asthma is clinically allergen-driven and/or
  - Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

Note: these are not the criteria for add-on biologic therapy (see 6b)

Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
- Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest, DLCO
- Skin prick testing or specific IgE for relevant allergens, if not already done
- Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion

Consider need for social/psychological support

Involves multidisciplinary team care (if available)

Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

Is add-on Type 2 biologic therapy available/affordable?

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

If add-on Type 2 biologic therapy is NOT available/affordable:
- Consider higher dose ICS, if not used
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LMLTRA, azithromycin)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

If no evidence of Type 2 inflammation:
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of LAMA or azithromycin (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
  - Consider bronchial thermoplasty (+ registry)

Not currently eligible for biologics
Assess and treat severe asthma phenotypes  

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria, comorbidities and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Check local eligibility criteria for specific biologic therapies as these may vary from those listed
Assess and treat severe asthma phenotypes  
Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria, comorbidities and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

**Anti-IgE**
- Is the patient eligible for anti-IgE for severe allergic asthma?
  - Sensitization on skin prick testing or specific IgE
  - Total serum IgE and weight within dosage range
  - Exacerbations in last year

  - no

**Anti-IL5 / Anti-IL5R**
- Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?
  - Exacerbations in last year
  - Blood eosinophils, e.g. ≥150/µL or ≥300/µL

  - no

**Anti-IL4R**
- Is the patient eligible for anti-IL4R for severe eosinophilic/Type 2 asthma?
  - Exacerbations in last year
  - Blood eosinophils ≥150/µL or FeNO ≥25 ppb

  - or because of need for maintenance OCS?

- no

Eligible for none?
Return to section 6a

*Check local eligibility criteria for specific biologic therapies as these may vary from those listed*
Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria,
- comorbidities and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

- Anti-IgE
  - Is the patient eligible for anti-IgE for severe allergic asthma?
    - Sensitization on skin prick testing or specific IgE
    - Total serum IgE and weight within dosage range
    - Exacerbations in last year
  - What factors may predict good asthma response to anti-IgE?
    - Blood eosinophils >250/μL ++
    - FeNO >20 ppb +
    - Allergen-driven symptoms +
    - Childhood-onset asthma +

- Anti-IL5 / Anti-IL5R
  - Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?
    - Exacerbations in last year
    - Blood eosinophils, e.g. >150/μL or >300/μL
  - What factors may predict good asthma response to anti-IL5/5R?
    - Higher blood eosinophils +++
    - More exacerbations in previous year +++
    - Adult-onset of asthma ++
    - Nasal polyposis ++

- Anti-IL4R
  - Is the patient eligible for anti-IL4R... for severe eosinophilic/Type 2 asthma?
    - Exacerbations in last year
    - Blood eosinophils >150/μL or FeNO >25 ppb
    - or because of need for maintenance OCS?
  - What factors may predict good asthma response to anti-IL4R?
    - Higher blood eosinophils ++
    - Higher FeNO +++

Eligible for none?
Return to section 6a

Check local eligibility criteria for specific biologic therapies as these may vary from those listed
Assess and treat severe asthma phenotypes cont’d

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2 targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria, comorbidities and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

- Anti-IgE
  - Is the patient eligible for anti-IgE for severe allergic asthma?
    - Sensitization on skin prick testing or specific IgE
    - Total serum IgE and weight within dosage range
    - Exacerbations in last year
  - What factors may predict good asthma response to anti-IgE?
    - Blood eosinophils ≥250/μl ++
    - FeNO ≥20 ppb +
    - Allergen-driven symptoms +
    - Childhood-onset asthma +
  - Extend trial to 6-12 months
  - Choose one if eligible; trial for at least 4 months and assess response

- Anti-IL5 / Anti-IL5R
  - Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?
    - Exacerbations in last year
    - Blood eosinophils, e.g. ≥150/μl or ≥300/μl
  - What factors may predict good asthma response to anti-IL5/5R?
    - Higher blood eosinophils +++
    - More exacerbations in previous year +++
    - Adult-onset of asthma ++
    - Nasal polyposis ++
  - Extend trial to 6-12 months
  - Choose one if eligible; trial for at least 4 months and assess response

- Anti-IL4R
  - Is the patient eligible for anti-IL4R for severe eosinophilic/Type 2 asthma?
    - Exacerbations in last year
    - Blood eosinophils ≥150/μl or FeNO ≥25 ppb
  - What factors may predict good asthma response to anti-IL4R?
    - Higher blood eosinophils +++
    - Higher FeNO +++

Eligible for none?
Return to section 6a

Check local eligibility criteria for specific biologic therapies as these may vary from those listed
Assess and treat severe asthma phenotypes  

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria, comorbidities and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE
Is the patient eligible for anti-IgE for severe allergic asthma?
- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year
  - no
  - yes

What factors may predict good asthma response to anti-IgE?
- Blood eosinophils ≥260/μl
- FeNO ≥20 ppb
- Allergen-driven symptoms
- Childhood-onset asthma

Anti-IL5/ Anti-IL5R
Is the patient eligible for anti-IL5/anti-IL5R for severe eosinophilic asthma?
- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/μl or ≥300/μl
  - no
  - yes

What factors may predict good asthma response to anti-IL5R?
- Higher blood eosinophils
- More exacerbations in previous year
- Adult-onset of asthma
- Nasal polyposis

Anti-IL4R
Is the patient eligible for anti-IL4R
- ... for severe eosinophilic/Type 2 asthma?
- Exacerbations in last year
- Blood eosinophils ≥150/μl or FeNO ≥25 ppb
  - no
  - yes

What factors may predict good asthma response to anti-IL4R?
- Higher blood eosinophils
- Higher FeNO

Eligible for none?
- Return to section 6a

Good asthma response?
- Choose one if eligible; trial for at least 4 months and assess response
- Extend trial to 6-12 months
- unclear

Good response to T2-targeted therapy?
- STOP add-on
- Consider switching to a different Type 2-targeted therapy, if eligible

Little/no response to T2-targeted therapy

Check local eligibility criteria for specific biologic therapies as these may vary from those listed
Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review response

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities
  - e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction
Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review response

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities
  - e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

If good response to Type 2-targeted therapy

- Re-evaluate the patient every 3-6 months
- For oral treatments: consider decreasing/stopping OCS first, then stopping other add-on medication
- For inhaled treatments: consider decreasing after 3-6 months; continue at least moderate dose ICS
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference
Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review response

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities
  - e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

If good response to Type 2-targeted therapy
- Re-evaluate the patient every 3-6 months
- For oral treatments: consider decreasing/stopping OCS first, then stopping other add-on medication
- For inhaled treatments: consider decreasing after 3-6 months; continue at least moderate dose ICS
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

If no good response to Type 2-targeted therapy
- Stop the biologic therapy
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
- Consider high resolution chest CT (if not done)
- Reassess phenotype and treatment options
  - Induced sputum (if available)
  - Consider add-on azithromycin
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchoscopy for alternative/additional diagnoses
  - Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies
- Do not stop ICS
Monitor / Manage severe asthma treatment

Continue to optimize management

7. Review response:
   - Asthma: symptom control, exacerbations, lung function
   - Type 2 comorbidities
     e.g. nasal polyposis, atopic dermatitis
   - Medications: treatment intensity, side-effects, affordability
   - Patient satisfaction

   If good response to Type 2-targeted therapy:
   - Re-evaluate the patient every 3-6 months
   - For oral treatments: consider decreasing/stopping OCS first, then stopping other add-on medication
   - For inhaled treatments: consider decreasing after 3-6 months; continue at least moderate dose ICS
   - Re-evaluate need for ongoing biologic therapy
   - Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

   If no good response to Type 2-targeted therapy:
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   - Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
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     - Consider bronchoscopy for alternative/additional diagnoses
     - Consider bronchial thermoplasty (+ registry)
   - Stop ineffective add-on therapies
   - Do not stop ICS

8. Continue to optimize management as in section 3, including:
   - Inhaler technique
   - Adherence
   - Comorbidity management
   - Patients' social/emotional needs
   - Two-way communication with GP for ongoing care

Notes:
Definition of severe asthma

- This has been clarified, and is now worded without reference to GINA Steps, since the treatments recommended at each step have changed over time.
- Severe asthma is asthma that is uncontrolled despite high dose ICS-long-acting beta$_2$ agonist (LABA), or that requires high dose ICS-LABA to remain controlled

Blood eosinophils for eligibility for biologic treatment

- The recommendation to repeat blood eosinophils if low at first assessment in a patient with severe asthma has been confirmed by a study that found that 65% of patients on medium or high dose ICS-LABA shifted their eosinophil category over a 12-month period (Lugogo et al, Ann Allergy Asthma Immunol 2020)
- For eligibility for biologic therapy, check the criteria specified by your local payer
- In the severe asthma decision tree, to avoid ambiguity, a second example of the eosinophil criteria used by different payers has been included (“e.g. $\geq 150$ or $\geq 300/\mu l$”)
Long-acting muscarinic antagonists (LAMAs)
- Previous recommendations for adding tiotropium to ICS-LABA have been expanded to include ICS-LABA-LAMA combinations (‘triple therapy’) for patients aged ≥18 years in Step 5, i.e. with LAMA added to medium or high dose ICS-LABA
- Adding LAMA to medium or high dose ICS-LABA provides a modest improvement in lung function, although not in symptoms, and in some studies, there was a small reduction in exacerbations

Add-on azithromycin (adults)
- Evidence from a new meta-analysis (Hiles et al, ERJ 2019), and concerns about antibiotic resistance, confirm the positioning of add-on azithromycin for patients aged ≥18 years with severe asthma, i.e. after referral in Step 5
- No specific evidence is available about efficacy of azithromycin when added to medium dose ICS-LABA
- Recommendations about ‘macrolides’ have been changed to ‘azithromycin’, as all of the evidence for macrolides in asthma is with azithromycin
GINA collaborated with Tomoko Ichikawa, MS (Institute for Healthcare Delivery Design, University of Illinois at Chicago, USA) and Hugh Musick, MBA (Institute for Healthcare Delivery Design, University of Illinois at Chicago, USA) in developing this severe asthma Pocket Guide.

Development of the pocket guide included interviews with GINA members, and GPs and specialists

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The severe asthma pocket guide can be downloaded or ordered from the GINA website, www.ginasthma.org

A GINA pocket guide on difficult to treat and severe asthma in children 6–11 years is under development