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

V2.0 April 2021

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No additions or changes may be made to slides.

The Global Initiative for Asthma (GINA)

- GINA was established by the **WHO** and NHLBI in **1993**
- To increase **awareness** about asthma
- To improve asthma **prevention** and **management** through a coordinated worldwide effort
- GINA is independent .approved in about 100 countries
- Practical focus: multiple flow-charts and tables
- The GINA strategy report **is updated every year**
- **Twice-yearly cumulative review of new evidence** across the whole asthma strategy
-
- 1st pub1995.1st major revision2000,AWD 2001.2002 annually, Control vs Severity 2005,
- Non profit organization 2008 .2nd major revision2014.3rd major revision 2019,4th key change 2021

About the GINA strategy

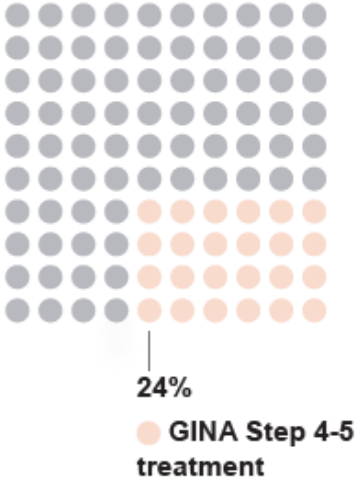
- The GINA report **is not a guideline**, but an **integrated evidence-based strategy** focusing on translation into clinical practice
- Recommendations **are framed**,, but as part of an integrated strategy, in relation to:
  - The GINA goals of preventing asthma deaths and exacerbations, as well as improving symptom control
  - Current understanding of underlying disease processes
  - **Human behaviour** (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'**
  - A survey of GINA Assembly members in 2017 strongly encouraged development of a **practical resource about severe asthma**

Terminology

- **Uncontrolled asthma**
  - **Frequent symptoms**(Night awaking ,Activity intolerance)
  - and/or flare-ups (**Frequent exacerbations**:1 time for Hospital admition,2 time for use of OCS)
  - 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 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 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**
  - i.e. relatively refractory to corticosteroids (rarely completely refractory)

How common is severe asthma?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?



These data are from a Dutch population survey of people ≥18 years with asthma[2]

How common is severe asthma?

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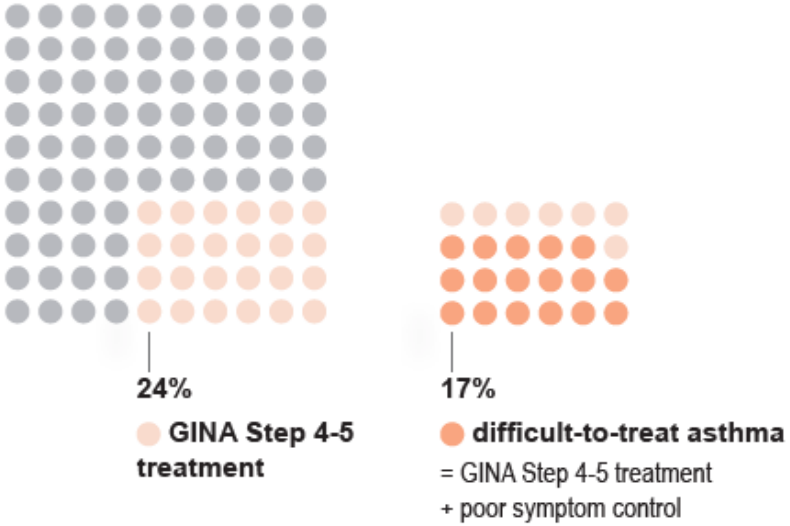

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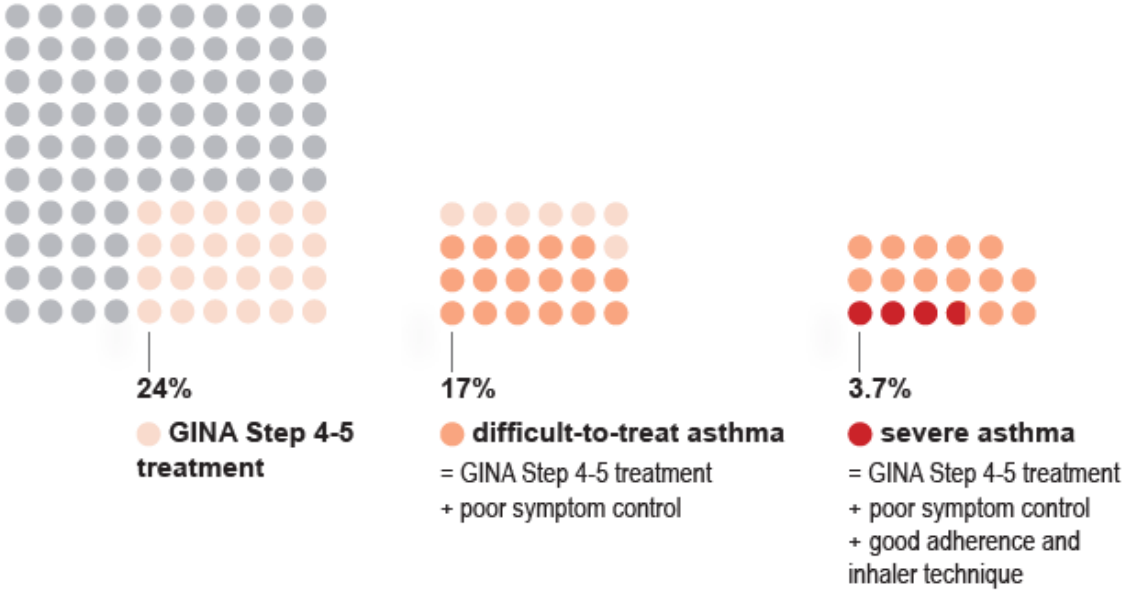

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Hekking et al, JACI 2015

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

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

Key

decision, filters

intervention, treatment

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DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

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

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- 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, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, if not used

Key

decision, filters

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- Consider trial of high dose ICS, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

yes → DIAGNOSIS: *"Severe asthma"* → If not done by now, refer to a specialist, if possible.

no → Consider stepping down treatment, OCS first (if used.)

Does asthma become uncontrolled when treatment is stepped down?

yes → Restore previous dose

no → Continue optimizing management

Key

- decision, filters
- intervention, treatment

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 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)

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yes

- 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)

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 tiotropium or macrolide* (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)

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 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
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- 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***)*

yes

- 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)

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

no

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, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

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)
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Not currently eligible for biologics

*Off-label

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

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

yes

- 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)

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

yes

no

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, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

no

- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
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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** 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 / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

no / *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?

Eligible for none?

Return to section **6a**

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

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:
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What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥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 ++

no / *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?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

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Assess and treat severe asthma phenotypes *cont'd*

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

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What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

Choose one if eligible; trial for at least 4 months and assess response

Good asthma response?

unclear → Extend trial to 6-12 months

yes → Good response to T2-targeted therapy

no

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

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Good asthma response?

yes → Good response to T2-targeted therapy

unclear → Extend trial to 6-12 months

no → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible

no → 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

yes →

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

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- Re-evaluate need for ongoing biologic therapy
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no

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 macrolide*
  - 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

**Off-label*

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Continue to optimize management

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- Stop ineffective add-on therapies
- Do not stop ICS

**Off-label*

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:

Thank you