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台灣嚴重氣喘診療共識

Taiwan Consensus Statement on the Diagnosis and Management of Severe Asthma

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第六章

嚴重氣喘的防治與處理

GLOBAL INITIATIVE FOR ASTHMA

GINA

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

Diagnosis and Management

A GINA Pocket Guide
For Health Professionals

V2.0 April 2019

台灣嚴重氣喘診療共識

- 專家提問: 12個重要問題
- 台灣嚴重氣喘共識- 會前會議: 2019/02/14
  - 王鶴健、詹明澄、許超群、林慶雄、林鴻詮、李崗遠、鄭世隆、柯信國、林聖皓
- 北中南分區共識會議
  - 北區: 2019/03/02
  - 中區: 2019/03/03
  - 南區: 2019/03/17
- 台灣嚴重氣喘共識- 結論整合會議: 2019/04/17
- 公開發表與討論: Post-ATS 2019/06/15
- 公開發行 (紙本與電子檔)

Severe Asthma Casebook

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手冊內容規劃:

章節	主題	作者	責任編輯
1	**Consensus Statement**		
	Consensus definition	許超群	王鶴健
	Diagnostic algorithm	詹明澄	王鶴健
2	**Clinical Cases (10-15 cases)**		
	Difficult-to-treat asthma		柯信國
	Severe allergic asthma		林聖皓
	Severe eosinophilic asthma		林慶雄
	Overlap phenotype		鄭世隆
	Severe neutrophilic asthma		李崗遠
	Paucigranulocytic asthma		林鴻詮

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Q1: Severe asthma 的uncontrolled 定義, 新版GINA difficult-to-treat and severe asthma與ERS/ATS Taiwan 版本有出入

ERS/ATS	GEMA
過去一年需要高劑量吸入性皮質類固醇(ICS)及第二種控制藥物包括長效型乙二型交感神經刺激劑(LABA)或白三烯素修飾劑(leukotriene modifier/茶鹼(theophylline) 或過去一年有≧50%時間需要全身性皮質類固醇 (systemic CS)	過去一年接受高劑量吸入性皮質類固醇/長效型乙二型交感神經刺激劑(ICS/LABA)組合治療或同樣時期間需要口服類固醇治療至少半年以上

2019 GINA Difficult-to-treat and severe asthma

- **Difficult-to-treat asthma** is asthma that is uncontrolled despite GINA Step 4 or 5 treatment (e.g. medium or high dose ICS with a second controller; maintenance OCS), or that requires such treatment to maintain good symptom control and reduce the risk of exacerbations. It does not mean a 'difficult patient'. In many cases, asthma may appear to be difficult-to-treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because the diagnosis is incorrect.
- **Severe asthma** is a subset of difficult-to-treat asthma. It means asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. At present, therefore, 'severe asthma' is a retrospective label. It is sometimes called 'severe refractory asthma' since it is defined by being relatively refractory to high dose inhaled therapy. However, with the advent of biologic therapies, the word 'refractory' is no longer appropriate. Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.

	2018 GINA Pocket Guide	2014 ERS/ATS
Uncontrolled asthma	• Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma), and/or • Frequent exacerbations (≥ 2/year) requiring oral corticosteroids (OCS), or serious exacerbations (≥ 1/year) requiring hospitalization	Uncontrolled asthma defined as at least one of the following: (1) Poor symptom control: ACQ consistently ≥1.5, ACT < 20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines) (2) Frequent severe exacerbations: two or more bursts of systemic CS (≥3 days each) in the previous year (3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year (4) Airflow limitation: after appropriate bronchodilator withhold FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
Difficult-to-treat asthma	• Uncontrolled despite GINA step 4 or 5 treatment, or that requires such treatment to maintain good symptom control and reduce risk of exacerbations • In many cases, asthma may appear difficult-to-treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because of the diagnosis is incorrect	Inherent in the definition of severe asthma is the exclusion of individuals who present with ‘‘difficult’’ asthma in whom appropriate diagnosis and/or treatment of confounders vastly improves their current condition (see the evaluation section). Therefore, it is recommended that patients presenting with ‘‘difficult asthma’’ have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for more than 3 months. Thus, severe asthma according to the ATS/ERS definition only includes patients with refractory asthma and those in whom treatment of comorbidities such as severe sinus disease or obesity remains incomplete.
Severe asthma	• Uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased • A retrospective label • Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed	Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS* and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥ 50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy (* high dose definition is different from GINA) Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma.

Q1: Severe asthma 的uncontrolled 定義, 新版GINA difficult-to-treat and severe asthma與ERS/ATS Taiwan 版本有出入

- **Central**
  - 採用GINA 2018 Pocket為定義
  - 由於GINA 2018 Pocket並未採用lung function來定義severe asthma，但poor lung function可以視為惡化的風險。
- **North**
  - 建議採用新版2018 GINA pocket guide定義，主要以症狀控制和AE來定義uncontrolled asthma，沒有包含肺功能的定義。並依照建議確認吸入劑使用技巧、服藥順從性、共病與排除modifiable factors、使用最佳化藥物等流程後，確認為difficult-to-treat asthma或severe asthma。

Q1: Severe asthma 的uncontrolled 定義, 新版GINA difficult-to-treat and severe asthma與ERS/ATS Taiwan 版本有出入

- **South**
  - 建議採用新版2018 GINA pocket guideline定義。
  - **Uncontrolled asthma :未控制氣喘定義**包含下列其中之一：1) **氣喘症狀控制不良**（臨床上常用ACT < 20） 2) **頻繁發作需使用口服類固醇**（每年最少兩次），**或需要住**院（每年最少一次）。若僅是fixed airway obstruction而不符合上述其中一項，則不應視為uncontrolled。
  - **Difficult-to-treat asthma**：接受GINA 第4階段以上治療（含使用維持性口服類固醇）仍然有**控制不良**症狀和 / 或急性發作。未控制/仍有症狀或急性惡化**可**能因為modifiable factor未控制所造成。例**如, 吸入器使用技巧、服藥順從性、吸菸及共病症等。另外要考慮診斷是否正確。**
  - **Severe asthma :** 排除modifiable factors後，仍需**接受** GINA **第4階段以上治療**才能達到良好控制（或仍無法控制）之Difficult-to-treat asthma。

Q2: 在使用生物製劑前是否一定要使用過LAMA? 還是某一種severe asthma族群才需要先使用LAMA (Tiotropium)？

- **Central**
  - 在使用生物製劑之前，建議嘗試使用ICS加上LABA/LAMA/LTRA，來達到最佳氣喘治療。
- **South**
  - 在使用生物製劑之前，建議應先嘗試使用LAMA。應注意目前LAMA用於氣喘治療，僅tiotropium有適應症。
- **North**
  - 強烈建議使用LAMA，而不是使用生物製劑前一定要使用過LAMA。可註記不使用的原因，例如肺功能正常無fixed airway obstruction、急性惡化次數等，不一定要先使用LAMA才能用生物製劑。

Q3. 是否需要使用high-dose ICS後才可以定義為severe asthma? GINA and ERS/ATS 對於high dose ICS定義也不同?

- **Central**
  - 同意應使用high dose ICS，其high dose ICS definition 採用台灣嚴重氣喘指引的版本。
- **South**
  - 考量GINA定義及臨床上high-dose ICS的選擇不多，建議使用medium-to-high dose ICS為定義severe asthma之標準。
  - 同意high-dose ICS為氣喘控制不良時之治療策略之一，醫師應盡可能嘗試是否能改善病人之氣喘控制。
  - ICS 劑量之定義建議以台灣氣喘指引之內容為標準。
- **North**

Q3. 是否需要使用high-dose ICS後才可以定義為severe asthma? GINA and ERS/ATS 對於high dose ICS定義也不同?

- **North**
  - 考量GINA定義，及臨床上也可能在增加ICS/LABA劑量前先評估是否加上其他治療，建議使用medium-to-high dose ICS為定義severe asthma之標準。
  - ICS 劑量之定義建議以台灣氣喘指引之內容為標準，guideline中未定義的ICS如fluticasone furoate、ultrafine beclomethasone可另外註記說明。

Q4. 診斷severe asthma 需要經過3-6個月SMART嗎?

- **Central**
  - ICS-formoterol maintenance and reliever therapy是達到 optimal treatment 的其中一種方式，在difficult-to-treat asthma 病患中，可考慮嘗試使用ICS-formoterol maintenance and reliever therapy，來達到最佳氣喘治療
- **South**
  - ICS-formoterol maintenance and reliever therapy是達到 optimal treatment 的其中一種方式，SMART並非診斷severe asthma時之必要條件。
- **North**
  - SMART是達到 optimal treatment 的其中一種方式，並非診斷 severe asthma時之必要條件。

Q5: When is the right timing to check EOS level? How frequently should we test EOS?

- **Central**
  - Initial
  - Uncontrolled
  - 需要定義Th2 inflammation (lowest OCS 抽三次)
- **South**
  - 初診斷時
  - Asthma uncontrolled，治療需要升階時
  - AE使用OCS前
  - 定期評估（例如每年）

Q5: When is the right timing to check EOS level? How frequently should we test EOS?

- **North**
  - 初始治療時
  - Asthma uncontrolled時
  - 給予口服類固醇前
  - 為了確認患者是non-Type 2 inflammation
  - 定期評估

Q6: If patients already use OCS, how to check the EOS to reflect the real data?

- **Central**
  - 將OCS 降到最低劑量時，建議抽三次。
- **South**
  - 病患使用OCS可能造成EOS降低，因此建議考慮於其他時間點進行檢測。
  - 若是常期使用OCS，建議減至最低劑量兩週後再測；若AE已使用OCS，建議AE四週後再測。
- **North**
  - 考慮OCS可能抑制EOS，建議於OCS降低至最低可能劑量時測量，根據情況可評估是否需要再次測量，依據2018 GINA pocket guide最多可測量三次。

Q7: Severe eosinophilic asthma OCS 要用多久才算控制不好?

- **Central**
  - 使用OCS 三個月都還控制不好，則應該及早介入生物製劑治療，使用OCS建議不超過三個月。
- **South**
  - 建議定義時應同時考慮OCS之劑量和使用時間：使用≥ 5 mg/day prednisolone，持續3個月仍有氣喘控制不良症狀或急性惡化即可定義為控制不好。
- **North**
  - OCS使用三個月的時間，應足夠可定義為控制不好。

Q8: 目前胸腔科醫師已鮮少長期使用口服類固醇，對於使用anti-IL5藥物之六個月長期類固醇規範是否可以放寬?

- **Central**
  - 建議OCS三個月即可
- **South**
  - 使用 ≥ 5 mg/day prednisolone持續至少3個月
- **North**
  - 同意應予以放寬

Q9: If current treatment is uncontrolled, how long and what items should we evaluate before diagnosing for severe asthma ?

- **Central**
  - 建議3-6的月即可，評估項目如GINA中指出：ACT、Peak flow、AE狀況（常急診、住院、使用口服類固醇）、共病、藥物使用順從性、暴露危險因子（抽煙,環境污染等..）、藥物副作用、情緒問題等。
- **South**
  - 建議治療3-6個月評估，評估項目如GINA中所述。建議可由學會製作公版check list供需要的醫師使用。
- **North**
  - 建議治療3-6個月評估，評估項目如GINA中所述。

Q10: 健保委員提出請證明該病患吸入器使用技巧良好並且藥物順從性佳，請問臨床上要如何提出證明for病患吸入器使用技巧已經良好且順從性佳?

- **Central**
  - 回診頻率紀錄
  - Inhaler technique and compliance check list
  - 已用上Air chamber亦可作為證明資料之一
- **South**
  - 同意會前會所決議之三項簡單check list
  - 各inhaler technique之check list（由學會提供版本，供需要時使用，並非強制使用）
  - 患者若已經加入氣喘照護計畫，且規律回診，應信賴該醫療團隊已盡可能的達成此兩項衛教

Q10: 健保委員提出請證明該病患吸入器使用技巧良好並且藥物順從性佳，請問臨床上要如何提出證明for病患吸入器使用技巧已經良好且順從性佳?

- **North**
  - 建議參考回診頻率紀錄，與學會提供check list供臨床醫師參考使用。

- 會前會議中建議之三項check list:
  - 病患及照護者是否自述或證實有常規吸藥
  - 醫師、衛教師或藥師是否已再次衛教，確認病患吸入方式正確
  - 是否於下次回診時親自檢查病患吸入器劑數窗格已歸零

Q11. 如果氣喘病人有GRED、COPD、肥胖、過敏等共病，要如何進行下一步的評估跟治療？請問要處理到什麼程度才算是排除共病呢?

- **Central**
  - 根據GINA對共病的定義擬定check list，並在病例上記載排除共病
- **South**
  - 建議對這些共病製作check list，提醒醫師評估。亦可提供GERD及OSA之相關問卷，供醫師評估這些共病時使用。
  - □ 肥胖
    □ 胃食道逆流 (GERD)
    □ 慢性鼻竇炎
    □ 阻塞型睡眠呼吸中止症 (OSA)
    □ 心臟病

Q11. 如果氣喘病人有GRED、COPD、肥胖、過敏等共病，要如何進行下一步的評估跟治療？請問要處理到什麼程度才算是排除共病呢?

- **North**
  - 建議提供最基本共病checklist協助醫師評估，包含2018 GINA pocket guide中有提到的obesity、GERD、chronic rhinosinusitis、OSA。
  - 此checklist供臨床醫師評估並記錄於病歷，表示應注意、有注意，評估與治療方式由臨床醫師決定。

Q12.診斷 Severe asthma 需包括評估SAD嗎?

- **Central**
  - GINA 定義的severe asthma並無需SAD，但在uncontrolled and difficult-to-treat 的病患可考慮SAD的評估與治療
- **South**
  - 目前臨床上不易檢測SAD，SAD亦非診斷severe asthma時之必要評估項目，僅作為提醒氣喘控制不佳之評估參考。
  - 若要檢測SAD，不建議採用MMEF，可考慮以RV/TLC、IOS或做dynamic Chest CT來進行評估。
- **North**
  - Guideline中對診斷severe asthma無要求評估SAD，非必要條件。可建議評估small airway disease問題。目前臨床上SAD評估方式沒有定論，IOS、RV/TLC、MMEF都為可行的評估工具。

Major issues in the diagnosis and management for severe asthma in Taiwan

Original	Suggestion
Q1: Severe asthma 的uncontrolled 定義和新版 difficult-to-treat and severe asthma與 ERS/ATS Taiwan 版本有出入 Q2: 在使用生物製劑前是否一定要使用過LAMA? 還是某一種severe asthma族群才需要先使用LAMA(Tiotropium)？ Q3. 是否需要使用high dose ICS後才可以定義為severe asthma? GINA and ERS/ATS 對於high dose ICS定義也不同? Q4. 診斷severe asthma 需要經過3-6個月SMART 嗎? Q5: When is the right timing to check EOS level? How frequently should we test EOS? Q6: If patients already use OCS, how to check the EOS to reflect the real data? Q7: Severe eosinophilic asthma OCS 要用多久才算控制不好? Q8: 目前胸腔科醫師已鮮少長期使用口服類固醇，對於使用anti-IL5藥物之六個月長期類固醇規範是否可以放寬? Q9: If current treatment is uncontrolled, how long and what items should we evaluate before diagnosing for severe asthma? Q10: 健保委員提出請證明該病患吸入器使用技巧良好並且藥物順從性佳，請問臨床上要如何提出證明for病患吸入器使用技巧已經良好且順從性佳? Q11. 如果氣喘病人有GRED、COPD、肥胖、過敏等共病，要如何進行下一步的評估跟治療？請問要處理到什麼程度才算是排除共病呢? Q12.診斷 Severe asthma 需包括評估SAD嗎?	Q1: What is the definitions of uncontrolled, difficult-to-treat and severe asthma? (Q1) Q2: How to evaluate patients with difficult-to-treat asthma before they were diagnosed as having severe asthma? (Q4, Q9, Q12) Q3: For patients with difficult-to-treat asthma, how to evaluate their inhaler techniques? (Q10) Q4: For patients with difficult-to-treat asthma, what comorbidities should be evaluated and corrected? (Q11) Q5: Can we make the diagnosis of severe asthma for patients without using high-dose ICS? (Q3) Q6: For patients with severe asthma, when is the right time to measure blood eosinophil counts? (Q5, Q6) Q7: For patients with uncontrolled severe asthma, what treatment options do we have? (Q2, Q8)

Q1: What are the definitions of uncontrolled, difficult-to-treat, and severe asthma?

- **Recommendation:**
  We recommend adopting the GINA definitions for uncontrolled asthma, difficult-to-treat asthma, and severe asthma.

- **Uncontrolled asthma:** one or both of the following
  - Poor symptom control: ACT < 20, ACQ consistently ≥1.5
  - Frequent exacerbations (≥ 2/year) requiring OCS, or serious exacerbations (≥ 1/year) requiring hospitalization

Q1: What is the definitions of uncontrolled, difficult-to-treat and severe asthma?

- **Difficult-to-treat asthma:**
  - Uncontrolled despite GINA step 4 or 5 treatment, or requires such treatment to maintain good symptom control and reduce risk of exacerbations.
  - In many cases, asthma may appear to be difficult-to-treat because of **modifiable factors** such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or incorrect diagnosis.
- **Severe asthma:**
  - Asthma remains difficult-to-treat (requiring GINA Step 4 or 5 treatment) after correction for modifiable factors (adherence, inhaler technique, comorbidity, obesity, smoking)
  - The diagnosis should be retrospectively made after 3-6 months of optimized treatment

Q2: What evaluations and managements should be performed in patients with difficult-to-treat asthma before making the diagnosis of severe asthma?

- **Recommendation:**
  We recommend confirming the diagnosis of asthma, checking and correcting inhaler technique and adherence, treating modifiable risk factors and comorbidities in patients with difficult-to-treat asthma before making the diagnosis of severe asthma.

Q3: For patients with difficult-to-treat asthma, how to check their inhaler technique and adherence?

- **Recommendation:**
  We recommend using a check list, including self-report from the patients and direct observation from the healthcare providers, to evaluate the inhaler technique and adherence.
  - Does the patient use the inhaler regularly?
  - Does the patient's inhaler technique re-confirmed by a trained medical provider?
  - Does the patient use a spacer (if needed)?

Q4: For patients with difficult-to-treat asthma, what comorbidities and other modifiable risk factors should be evaluated and corrected?

- **Recommendation:**
  We recommend using a check list to evaluate the modifiable risk factors, including smoking status, exposures to environmental tobacco, allergens, indoor and outdoor air pollutions. We also recommend using a check list to evaluate comorbidities, including GERD, COPD, OSA, cardiac disease, bronchiectasis, chronic rhinosinusitis, anxiety and depression, obesity.

Q5: Can we make the diagnosis of severe asthma for patients without using high-dose ICS?

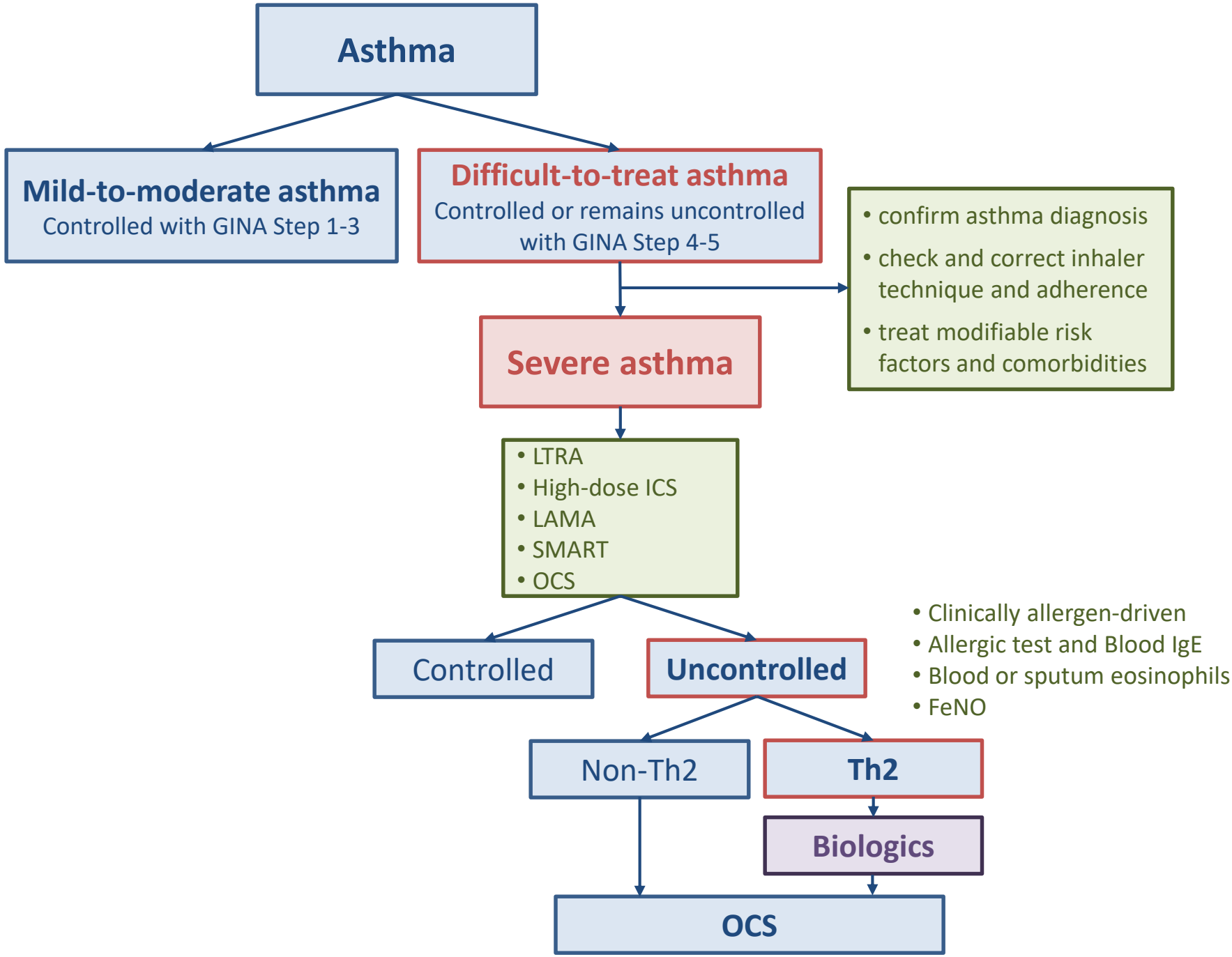
- **Recommendation:**
  We recommend the diagnosis of severe asthma is made when using at least medium-dose inhaled corticosteroid. The estimated clinical comparability of inhaled corticosteroids is based on Taiwan Asthma Guideline.
  - By definition, using high-dose ICS is not a required criteria for the diagnosis of severe asthma
  - High-dose ICS is a treatment option for severe asthma

Q6: For patients with severe asthma, when is the right time to measure blood eosinophil counts?

- **Recommendation:**
  We recommend measuring blood eosinophil counts when: (1) initiating treatment, (2) asthma uncontrolled, (3) before using systemic steroids. Also, we recommend repeating measurement of blood eosinophil count for up to 3 times before defining a non-Type 2 asthma.
  - When patients are using oral corticosteroid, we recommend measuring blood eosinophil at least 2 weeks at lowest dose of oral corticosteroid, or 4 weeks after acute exacerbation.

Q7: For patients with uncontrolled severe asthma, what treatment options do we have?

- **Recommendation:**
  We recommend maximize non-biological treatment before using biological agents.
  - Non-pharmacological interventions: smoking cessation, physical exercise, healthy diet, weight loss, mucus clearance strategies, influenza vaccination, and allergen avoidance.
  - Non-biological add-on therapy: high-dose ICS, LAMA (Tiotropium), leukotriene antagonist, ICS-formoterol maintenance and reliever therapy, and OCS.
  - For severe asthma patients with Th2 phenotype, add-on biological agents (anti-IgE and anti-IL-5/IL-5R) is highly recommended for those needing OCS or experiencing repeated exacerbation.


Asthma
Mild-to-moderate asthma
Controlled with GINA Step 1-3
Difficult-to-treat asthma
Controlled or remains uncontrolled with GINA Step 4-5
• confirm asthma diagnosis
• check and correct inhaler technique and adherence
• treat modifiable risk factors and comorbidities
Severe asthma
• LTRA
• High-dose ICS
• LAMA
• SMART
• OCS
Controlled
Uncontrolled
• Clinically allergen-driven
• Allergic test and Blood IgE
• Blood or sputum eosinophils
• FeNO
Non-Th2
Th2
Biologics
OCS