兒童氣喘診斷與治療趨勢

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CONTENT

定義與現況：兒童氣喘

兒童氣喘的臨床診斷

兒童氣喘的評估與治療

生物製劑

急性惡化的處置

兒童氣喘的日常預防建議

氣喘的基本定義

呼吸道阻塞和呼吸道對誘發因子（如運動、過敏及病毒感染）的過度反應以及慢性發炎，因此產生間歇性症狀且反覆發作 [1]

氣道過度敏感 [2]

遇到各種內因性或外因性的刺激時便會導致過度的支氣管收縮

反覆性氣道阻滯 [2]

(1)急性支氣管收縮
(2)氣道壁的腫脹
(3)慢性的黏液栓塞
(4)氣道壁的變形

- **兒童的氣喘臨床症狀多變且非特異性，病理特徵往往無法常規地被評估 [3]**

1. Illi S,et al. Lancet 2006;368:763–70; **2.** 臺灣氣喘衛教學會-兒童氣喘診療指引;
3. Larsen GL. J Allergy Clin Immunol. 2000;106(Suppl.):S153-7.

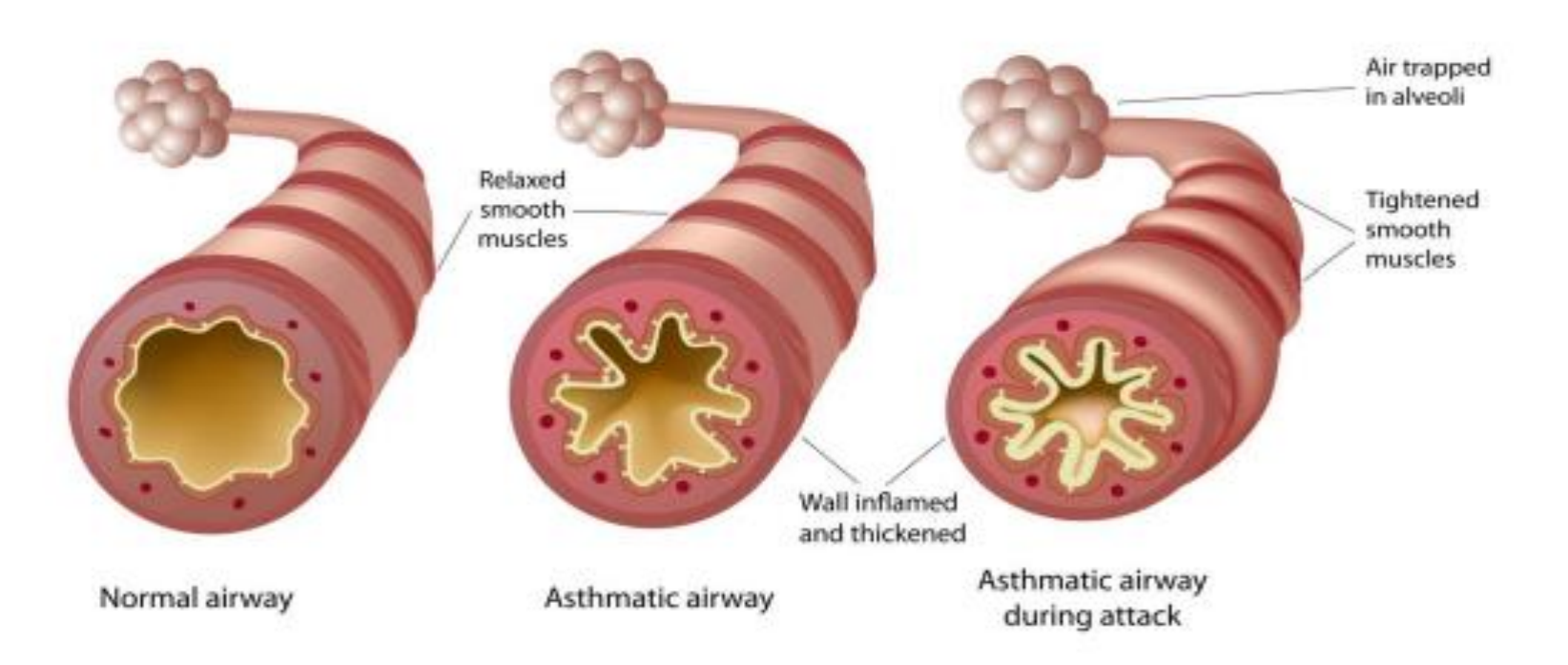
Introduction of asthma

- Airway inflammation, obstruction, hyper-responsiveness
- Triggers:
  - **Environmental allergens：pollens, molds, dust mite or animal dander**
  - **Viral respiratory infections**
  - **Changes in weather, cold air**
  - **Irritants such as tobacco smoke, air pollution, paints, etc.**
  - **Exercise**

Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma (GINA) Strategy 2022

Introduction of asthma

- Definition: Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation



Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma (GINA) Strategy 2022

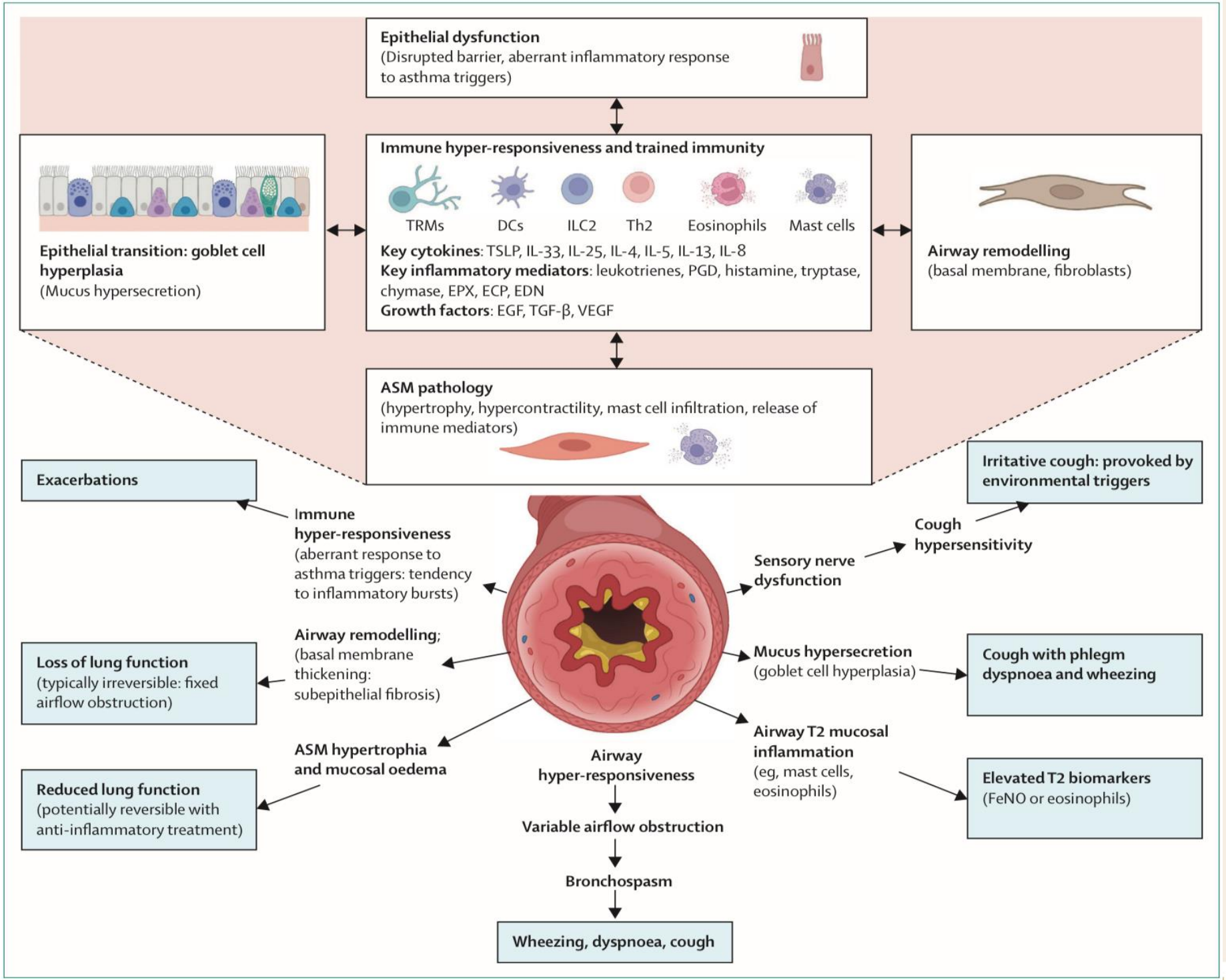
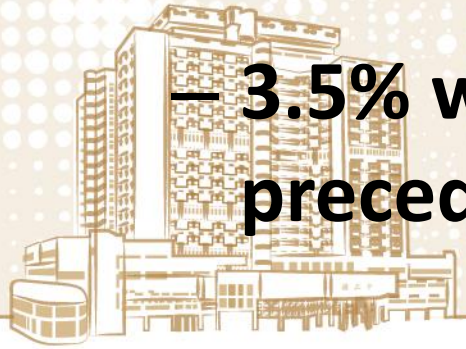


Figure 1: **Key pathophysiological mechanisms of asthma and resulting disease components and clinical features**

Lancet 2023; 401: 858–73

氣喘的盛行率

- **Asthma affected an estimated 262 million people in 2019 [1]and caused 455 000 deaths**
- **Taiwan (Global Asthma Network phase 1 survey)[2] in 13-14 y/o**
  - **Physician-diagnosed asthma: 12.4%.**
  - **Current wheezing was 9.2% (2017) (5.2% in 1995 and 7.0% in 2001)**
  - **Severe asthma symptoms: 3.3%**
  - **3.5% were admitted to hospitals within the preceding 12 months**



1. Lancet. 2020;396(10258):1204-22
2. World Allergy Organ J. 2023 Jul 14;16(7):100794

World Allergy Organization Journal
Volume 16, Issue 7, July 2023, 100794

Prevalence, associated factors, and impact of adolescent asthma in Taiwan: Global Asthma Network phase I survey

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盛行率男生較高

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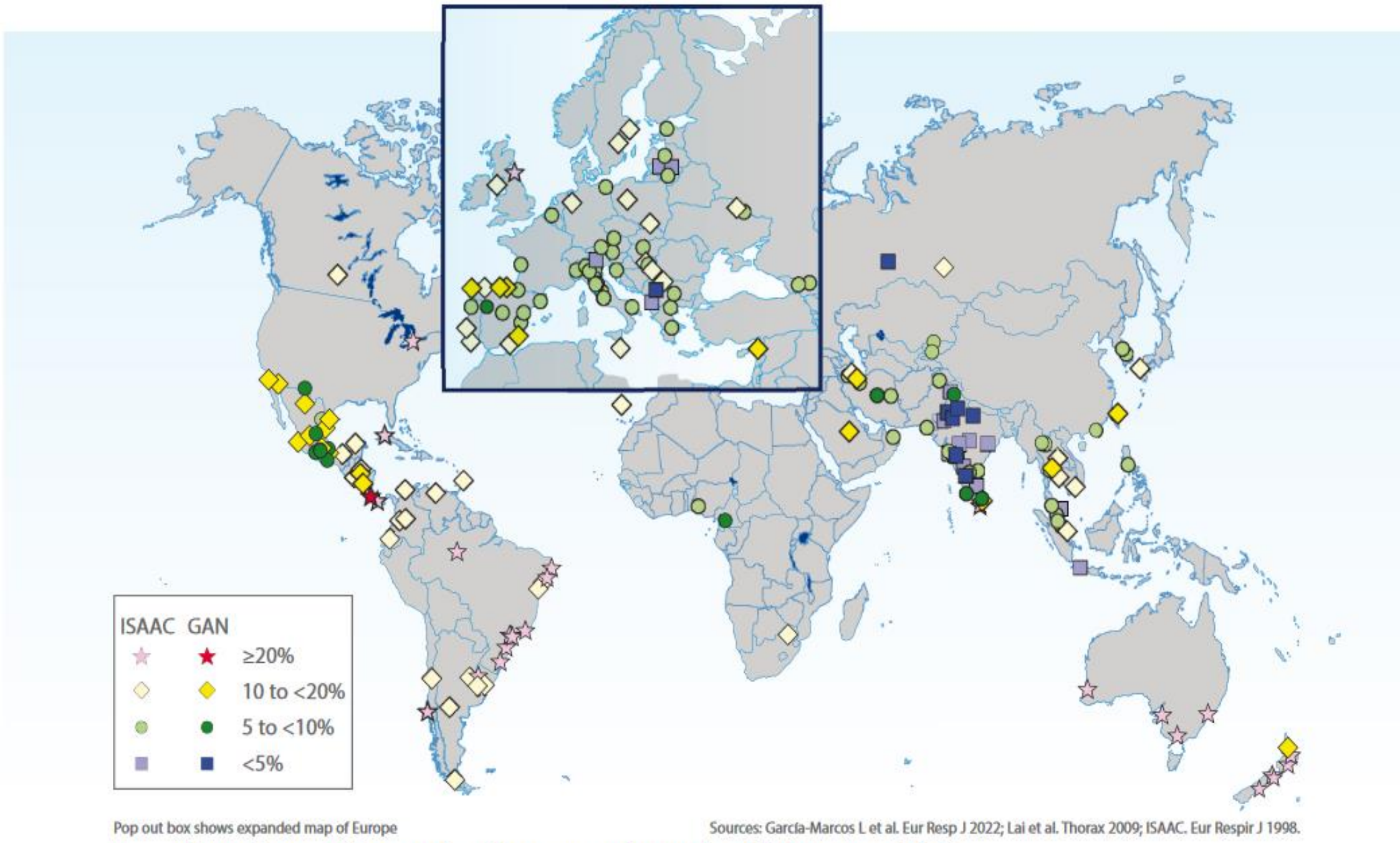
Items	Total			Male		Female		*P*-value
	Number	Percentage	(95% CI)	Number	Percentage	Number	Percentage	(male vs. female)
Total	3474	100%		1762[b]		1601[b]		
Asthma symptoms in the past 12 months								
Wheezing, current	321	9.2%	(8.2%–10.2%)	172	9.8%	135	8.4%	0.16
Wheezing attacks								0.02
1 to 3	227	6.5%	(5.7%–7.3%)	112	6.4%	107	6.7%	
4 to 12	62	1.8%	(1.4%–2.2%)	43	2.4%	18	1.1%	
More than 12	21	0.6%	(0.3%–0.9%)	13	0.7%	8	0.5%	
Wheezing that disturbed sleep								0.51
<1 per week	79	2.3%	(1.8%–2.8%)	39	2.2%	34	2.1%	
≥1 per week	16	0.5%	(0.3%–0.7%)	10	0.6%	6	0.4%	
Severe wheezing that limited speech	74	2.1%	(1.6%–2.6%)	49	2.8%	24	1.5%	0.01
Severe asthma symptoms[a]	115	3.3%	(2.7%–3.9%)	94	5.3%	47	2.9%	<0.01
Asthma ever	494	14.2%	(13.0%–15.4%)	284	16.1%	195	12.2%	<0.01
Asthma diagnosed by physicians	431	12.4%	(11.3%–13.5%)	253	14.4%	164	10.2%	<0.01
Exercise-induced wheezing	870	25.0%	(23.6%–26.4%)	477	27.1%	364	22.7%	<0.01
Nocturnal cough	963	27.7%	(26.2%–29.2%)	470	26.7%	462	28.9%	0.15

Taiwan: 10-20 % in GAN(Global Asthma Network) survey (age 6-7)

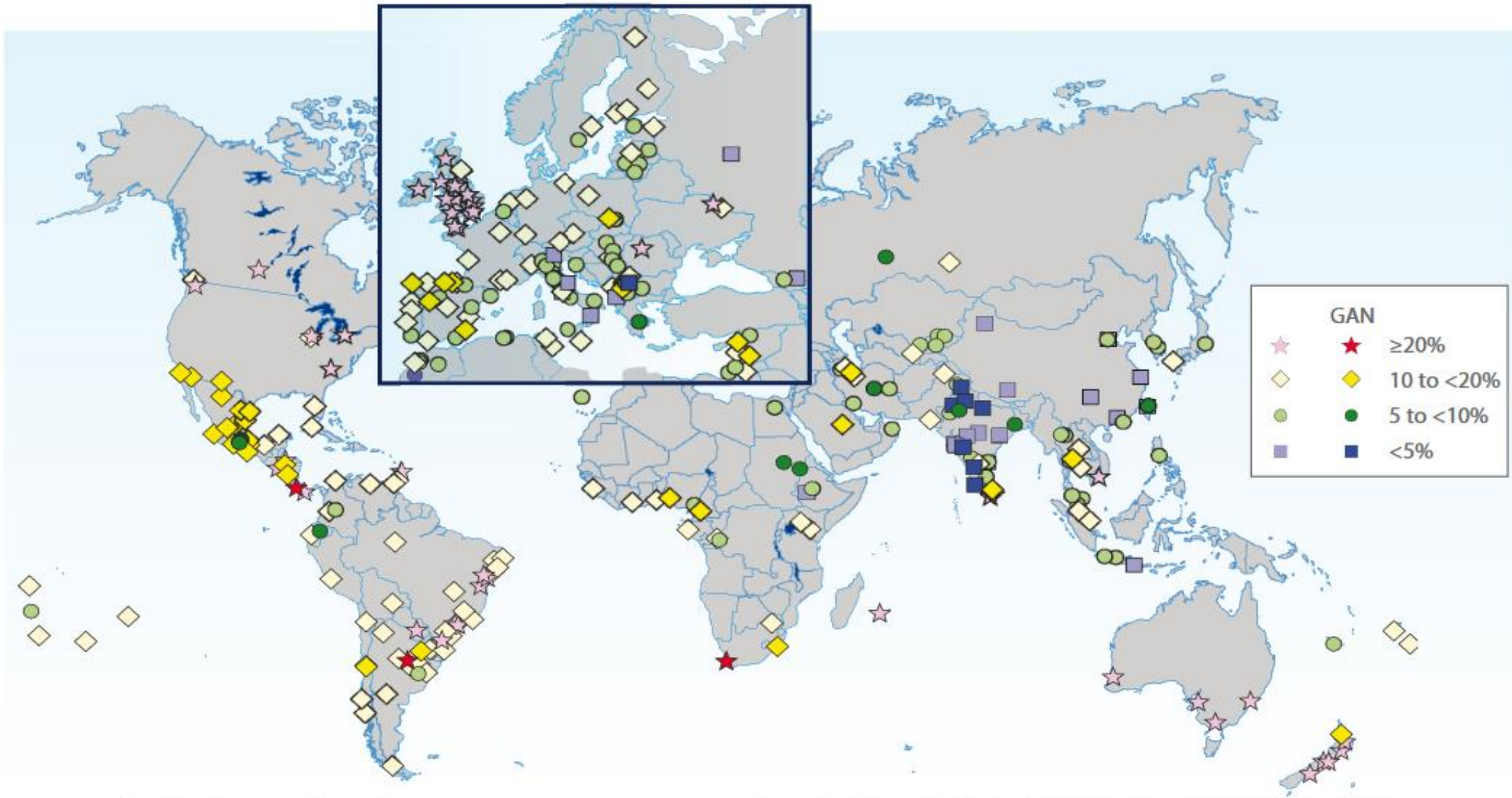


Pop out box shows expanded map of Europe

Sources: García-Marcos L et al. Eur Resp J 2022; Lai et al. Thorax 2009; ISAAC. Eur Respir J 1998.

Figure 1: Prevalence of current asthma symptoms in children aged 6-7

Taiwan: 5-10 % in GAN(Global Asthma Network) survey (age 13-14)



Pop out box shows expanded map of Europe

Sources: García-Marcos L et al. Eur Resp J 2022.; Lai et al. Thorax 2009; ISAAC. Eur Respir J 1998.

Figure 2: Prevalence of current asthma symptoms in adolescents aged 13-14

Taiwan: 5-10 % in GAN(Global Asthma Network) survey (adult)

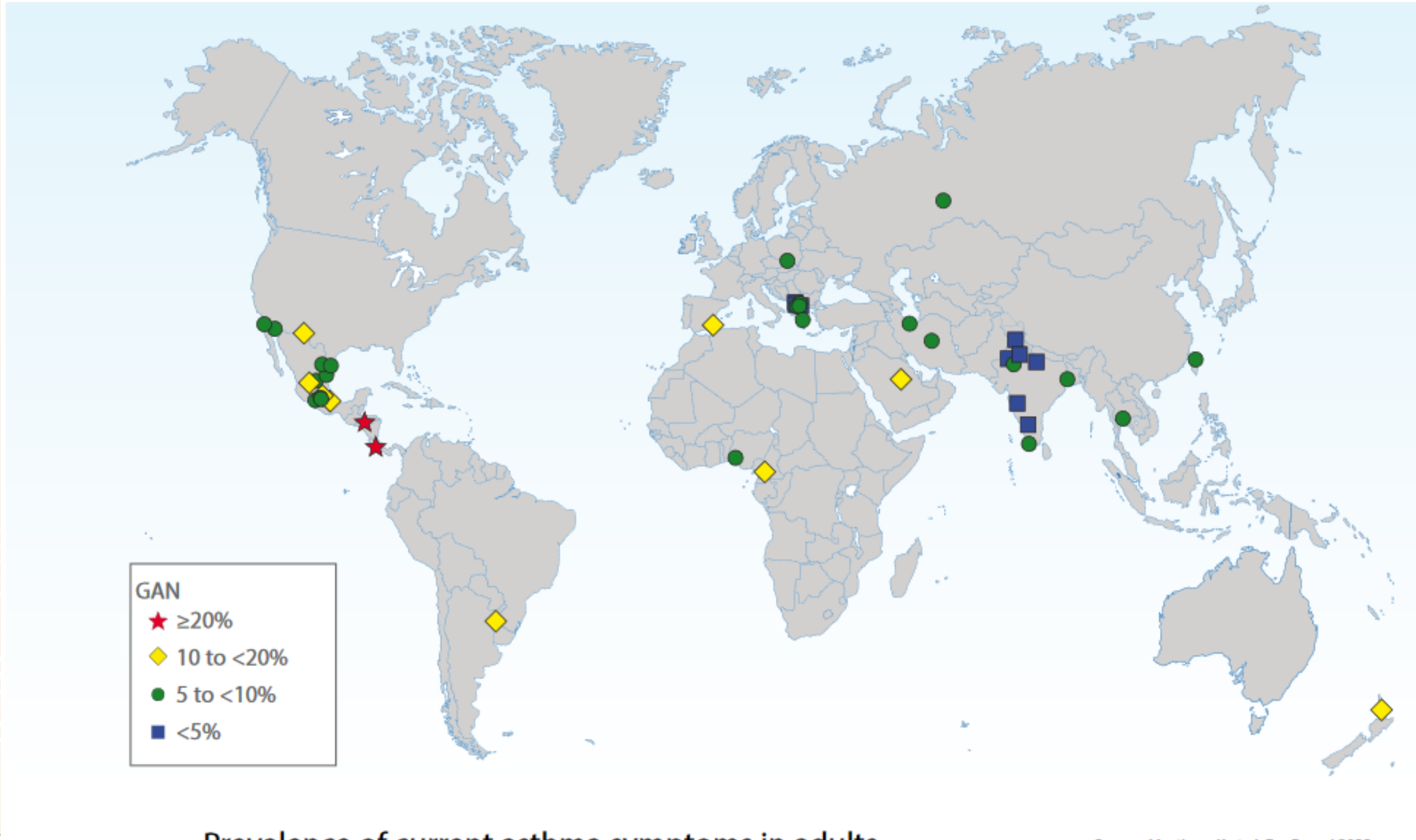


Figure 3: Prevalence of current asthma symptoms in adults

Source: Mortimer K et al. Eur Resp J 2022.

兒童氣喘年齡區段

國際氣喘診療指引將氣喘治療分為成人與兒童，各自有適用之診療標準[1,2]，但學齡前兒童因其氣喘症狀有時在步入學齡後會自主消失[3]，且治療方式較為特殊將獨立討論；另青少年氣喘的診斷標準與成人同，本次將不列入討論。

未成年族群	年齡區段[1,2]
學齡前兒童	≤ 5 歲
學齡兒童	6-11 歲
青少年	12-18 歲

1. Global Initiative for Asthma. 2020 GINA Report, Global Strategy for Asthma Management and Prevention
2. British Thoracic Society. 2016 BTS/SIGN Guideline for the management of asthma
3. Illi S,et al. Lancet 2006;368:763–70.

兒童和成人氣喘的比較

特性	兒童氣喘 V. S. 成人氣喘的比較
發生率	學齡前兒童的發生率高於成人
氣喘的模式	嚴重氣喘病童病情進展快速且頻繁，嚴重度較不穩定，但緩解的可能性較高。以 eosinophillic phenotype 為主
性別	嚴重氣喘病童以男性居多，成人則以女性居多
對類固醇的敏感性	體外淋巴球試驗結果顯示，兒童對於類固醇抑制發炎反應的效果較成人佳
肺功能	嚴重氣喘病童與成人相比，肺功能惡化比例較低。然而，即使具有較佳的肺功能，嚴重氣喘病童其肺功能變差的程度有高於成人之傾向

CONTENT

兒童氣喘的臨床診斷

- 6-11 歲
- 5歲以下

(1) 6-11 歲兒童氣喘臨床診斷-呼吸道病史

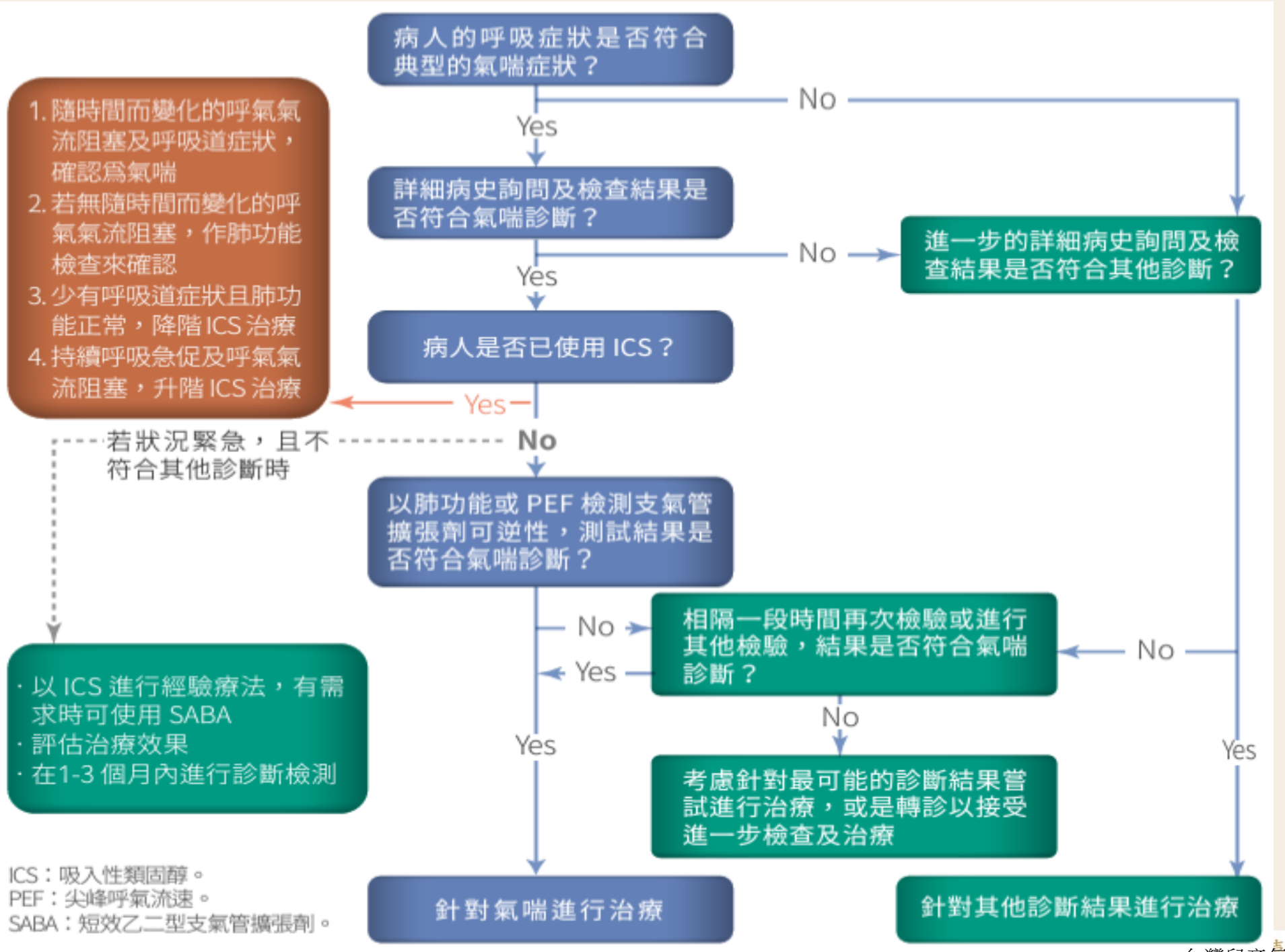
呼吸症狀隨時間而變化

典型的症狀包含**喘鳴、呼吸短促、胸悶、咳嗽**

- 氣喘病人通常不只一種症狀(尤其＞＝兩種時要高度懷疑）
- 症狀發生的頻率及強度皆隨著時間而有所變化
- 症狀常在夜間及行走時發生，或在這些時候特別嚴重
- 症狀常因運動、大笑、接觸到過敏原或冷空氣而觸發
- 病毒感染常會引發症狀，或讓症狀惡化

Global Initiative for Asthma. 2020 GINA Report, Global Strategy for Asthma Management and Prevention.

6-11 歲兒童氣喘的臨床診斷流程



ICS：吸入性類固醇。
PEF：尖峰呼氣流速。
SABA：短效乙二型支氣管擴張劑。

6-11 歲兒童氣喘臨床診斷-呼氣限制

證據顯示出現呼氣限制，且其程度隨時間而變化

- 診斷過程中應該至少出現一次下列情況：當 FEV_1 較低時，病人之 FEV_1/FVC 比值亦有所下降。兒童族群正常為 **> 0.90 (成人 > 0.75)**
- 檢測結果顯示肺功能的波動程度超過一般人，例如：
  - 吸入支氣管擴張劑後 FEV_1 增加幅度**超過預測值(baseline)的 12%**；此情形便稱作「支氣管擴張劑可逆性」
  - 每天日間(例: 早晚的差異) PEF 的**變化幅度 > 13% (成人 > 10%)**
  - 在沒有呼吸道感染的情況下，抗發炎治療 4 週後，FEV_1 和治療前相比增加幅度**超過預測值的 12%**

Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

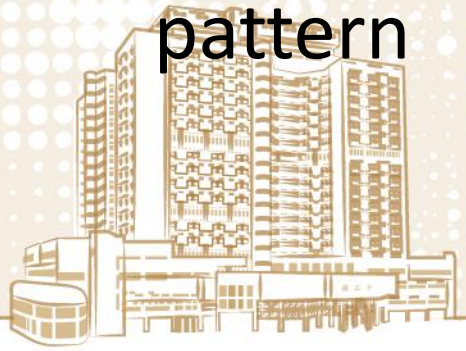
6-11 歲兒童氣喘臨床診斷-呼氣限制

證據顯示出現呼氣限制，且其程度隨時間而變化

- 波動程度愈大，或是波動頻率愈高，愈能確認診斷為氣喘。
- 應於症狀發生時、清晨、以及停用支氣管擴張劑後重複進行檢測。
- 在嚴重惡化或病毒感染期間，支氣管擴張劑可逆性可能會消失。若初次檢測時未出現支氣管擴張劑可逆性，應考量臨床上的急迫性以及是否可進行其他檢測方式，來決定下一步應採用何種診斷方式。

(2) 5 歲以下兒童氣喘臨床診斷

- Making a confident diagnosis in children 5 years and younger may be challenging due to:
  - Respiratory symptoms such as wheezing and cough are also common in children without asthma (especially < 2 y/o)
  - Routine assessment of airflow limitation or bronchodilator responsiveness is not plausible
  - **Probability-based approach** according to symptom pattern



Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma (GINA) Strategy 2022

(2) 5 歲以下兒童氣喘臨床診斷

- 因5 歲以下兒童不易取得確切診斷，應關注氣喘症狀的症狀或病史之**頻率及嚴重程度**：
  - 反覆喘鳴（**wheezing)/咳嗽**
  - 夜間咳嗽或睡眠時呼吸喘
  - 呼吸道感染發作
  - 異位性體質（異位性皮膚炎）遺傳或氣喘家族史

(2) 5 歲以下兒童氣喘臨床診斷

- 因5 歲以下兒童不易取得確切診斷，應關注氣喘症狀的症狀或病史之**頻率及嚴重程度**：
  - **暴露環境因子，如：二手菸、寵物、潮濕、黴菌等發病**
  - **運動(大哭吵架)或活動後發病**
  - **跟同齡兒童比活動力較差**
  - **使用控制藥物改善,停藥後惡化**

5 歲以下兒童氣喘的輔助檢測

- 成人的肺功能檢測普遍並不適用於 5 歲以下兒童，故可考慮改採以下方式協助確診：
  - **診斷性治療（therapeutic trial）**，利用 SABA 或低劑量的 ICS 進行為期 2-3 個月的診斷性治療或許可協助氣喘確診；建議可反覆進行以確定診斷。
  - **異位性體質測試**，可利用皮膚試驗或檢測抗原專一性的 IgE 來評估敏感性體質的程度；滿 3 歲之後，氣喘兒童通常都併有異位性體質; **檢測出過敏原是預測氣喘的最佳因子 (Early allergen sensitization increases the likelihood that wheezing children develop into persistent asthma)**

5 歲以下兒童氣喘的輔助檢測

- 成人的肺功能檢測普遍並不適用於 5 歲以下兒童，故可考慮改採以下方式協助確診：
  - **胸部 X 光**，可利用含 X 光在內的影像學檢查來排除生理結構異常，結核病，異物吸入造成類似氣喘症狀可能
  - **肺功能檢測**（4-5 歲幼童經有經驗的人員適當指引或許可進行）
  - **FeNO** (呼氣一氧化氮濃度試驗)主要還是研究使用，在呼吸道感染後四週如果FeNO 升高可以預測氣喘的發生

氣喘預測指標（Asthma Predictive Index）

改良式氣喘預測指標（mAPI）

尤其供 3 歲以下幼童診斷用參考

過去一年內曾發生 4 次(含 4次) 以上喘鳴惡化，其中至少 1 次發作經醫師確認
同時符合下列至少 **1 項主要**條件或 **2 項以上次要**條件

主要條件，以下至少 1 項

- 雙親病史：例如母親兒時曾罹患氣喘或父親有運動誘發型氣喘
- 醫師確診之**異位性皮膚炎（濕疹）**
- 對空氣中的過敏原敏感型**過敏：塵蟎**、貓、狗、黴菌、花草樹木等

次要條件，以下至少 2 項

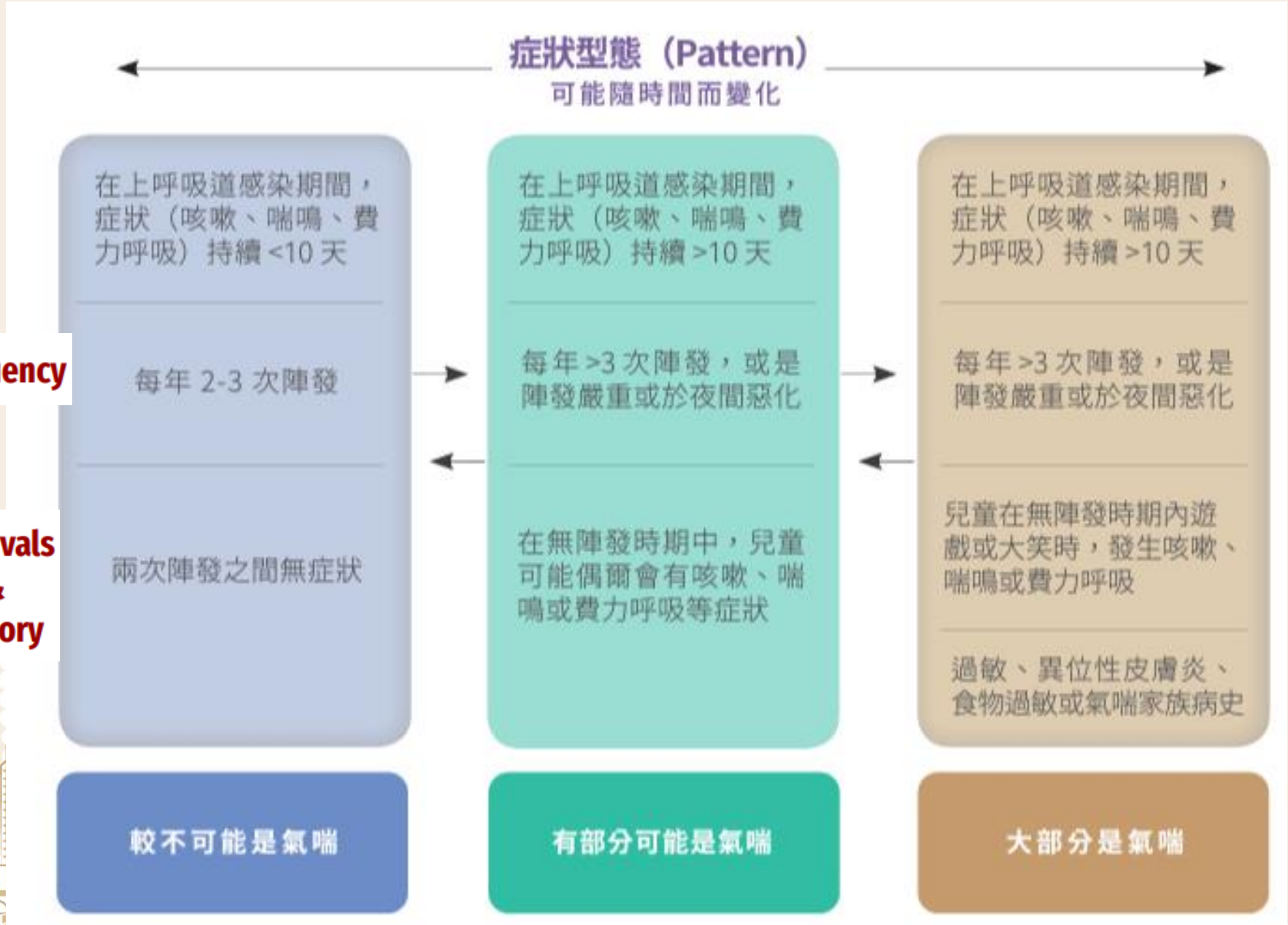
- 對**食物**敏感型過敏：牛奶、蛋或花生等（皮膚或血液檢驗結果陽性）
- 與感冒無關的喘鳴
- 血中嗜酸性球佔白血球比例 ≥ 4%
- 有過敏性鼻炎

陽性指標：76% 的學齡後氣喘罹病風險(4-10倍風險)
陰性指標：95% 的機率在學齡後不會再發氣喘

Castro-Rodriguez JA. J Allergy Clin Immunol. 2010;126:212-6.

狗牙根(鐵線草;Bermuda Grass)

5 歲以下喘鳴兒童的氣喘診斷可能性



台灣兒童氣喘診療指引 2023

兒童什麼情況（尤其五歲以下）有需要作進一步診斷　(可能不是氣喘)　?

- 長不大**(Failure to thrive)**
- 新生兒階段或很小就出現症狀
- 呼吸道症狀合併嘔吐
- 持續性喘鳴聲**(wheezing)**
- 對氣喘藥物反應不佳
- 跟典型的誘發因子(例如病毒性上呼吸道感染)無關聯
- 檢查到局部**(focal signs)**肺部,心血管的病徵或有杵狀指**(clubbing finger)**
- 沒有病毒感染時也有低血氧**(hypoxemia)**

6-11 歲兒童氣喘相似症狀的鑑別診斷

病症	症狀
慢性上呼吸道咳嗽症候群	打噴嚏、發癢、鼻塞、清喉嚨
吸入異物	突發症狀、單側出現喘鳴
支氣管炎	反覆感染、咳嗽有痰
原發性纖毛運動障礙	反覆感染、咳嗽有痰、鼻竇炎
先天性心臟病	心雜音
支氣管肺發育不全	早產、出生後即出現症狀
囊狀纖維化症	頻繁咳嗽，產生大量黏液、腸胃道症狀, 長不大

5歲以下兒童氣喘相似症狀的鑑別診斷

病症	症狀
反覆病毒上呼吸道感染	小於十天的咳嗽鼻塞，不同感染期間無症狀
胃食道逆流	餵食時咳嗽,反覆肺部感染，大量進食後容易嘔吐；對氣喘用藥反應不佳
吸入異物	在進食或遊戲時突發嚴重咳嗽或出現喘鳴聲、單側出現喘鳴，反覆肺部感染及咳嗽
氣管軟化症	通常從出生就有症狀，進食或哭泣時呼吸聲吵雜
肺結核	接觸史,對氣喘及一般抗生素藥物反應不佳
持續性細菌性支氣管炎	持續咳嗽有痰，對氣喘藥物反應不佳
原發性纖毛運動障礙	反覆感染、咳嗽有痰、鼻竇炎
先天性心臟病	心雜音,對藥物反應不佳，長不大，心搏過速或肝腫大
支氣管肺發育不全	早產、出生後即出現症狀
囊狀纖維化症	頻繁咳嗽，產生大量黏液、腸胃道症狀，長不大

CONTENT

兒童氣喘的評估與治療

治療前提：告知氣喘診斷之重要性

- 即使在英國, 仍有25%的 5-16 歲氣喘病童雖然有持續處方氣喘用藥, 但是沒下氣喘診斷, 這些病童有較多的急性發作, 有38% 氣喘症狀控制不佳(cACT < 19) [1]
- 這些病童用藥順從性較差, 也沒有management action plan/ risk recognition, 急診的醫師也比較不會很嚴肅看待

1. Thorax 2020;75:102–8

兒童的氣喘控制環

- 藥物治療
- 非藥物治療
- 治療可矯治危險因子
- 衛教及技巧訓練

- 症狀
- 急性發作
- 副作用
- 肺功能
- 共病
- 家長 / 監護人滿意度

- 確定診斷
- 症狀控制及危險因子評估
- 吸入器的使用技巧以及遵囑性
- 家長 / 監護人偏好

Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

氣喘控制狀況之評估： 氣喘症狀的控制程度

A. 氣喘症狀的控制程度

指標	氣喘控制程度		
	控制良好	部分控制	未獲控制
過去 4 週是否有下症狀？ ● 日間症狀超過每週 2 次 ● 日常活動因爲氣喘而受到限制 ● 曾因氣喘而夜間醒來 ● 需要 SABA 緩解型藥物*超過每週 2 次	沒有出現左列任何一項	出現 1-2 項	出現 3-4 項

* 運動前所使用的 SABA 緩解型藥物除外。

台灣兒童氣喘診療指引|2023

氣喘控制狀況之評估：導致氣喘病人臨床療效不佳的危險因子（6 歲以上）

可能導致未來幾個月內氣喘發作（惡化）的危險因子

- 氣喘症狀控制不佳
- 過去 1 年曾發生 1 次以上的嚴重惡化; 曾經發作需要插管或住加護病房
- 很常需要用到SABA(短效支氣管擴張劑); 較高的支氣管擴張劑可逆性
- 暴露：二手菸、室外或室內空氣污染、室內過敏原
- 合併肥胖，慢性鼻竇炎, 食物過敏幼童本身或其家庭有重大心理或社會經濟問題

可能引發不可逆之氣流受阻（fixed airflow limitation）的危險因子

- 早產, 低體重, 嬰兒時期體重增加太多；剛開始FEV1 較低
- 暴露：二手菸, 有毒化合物

可能引發藥物副作用的危險因子

- 全身性：經常使用口服型類固醇，或使用高劑量 ICS
- 局部性：使用中 / 高劑量 ICS；吸入器使用方式不正確；使用噴霧型 ICS 或面罩式輔助器時未保護皮膚或眼睛

Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

氣喘控制狀況之評估：導致氣喘病人臨床療效不佳的危險因子（5 歲以下）

可能導致未來幾個月內氣喘發作（惡化）的危險因子

- 氣喘症狀控制不佳
- 過去 1 年曾發生 1 次以上的嚴重惡化
- 容易發作的季節剛開始(特別是秋天)
- 暴露：二手菸、室外或室內空氣污染、室內過敏原
- 幼童本身或其家庭有重大心理或社會經濟問題
- 吸入器使用方式不正確, 不規則用藥

可能引發不可逆之氣流受阻（fixed airflow limitation）的危險因子

- 曾經發作需要住院
- 急性細支氣管炎病史

6-11 歲兒童氣喘的治療

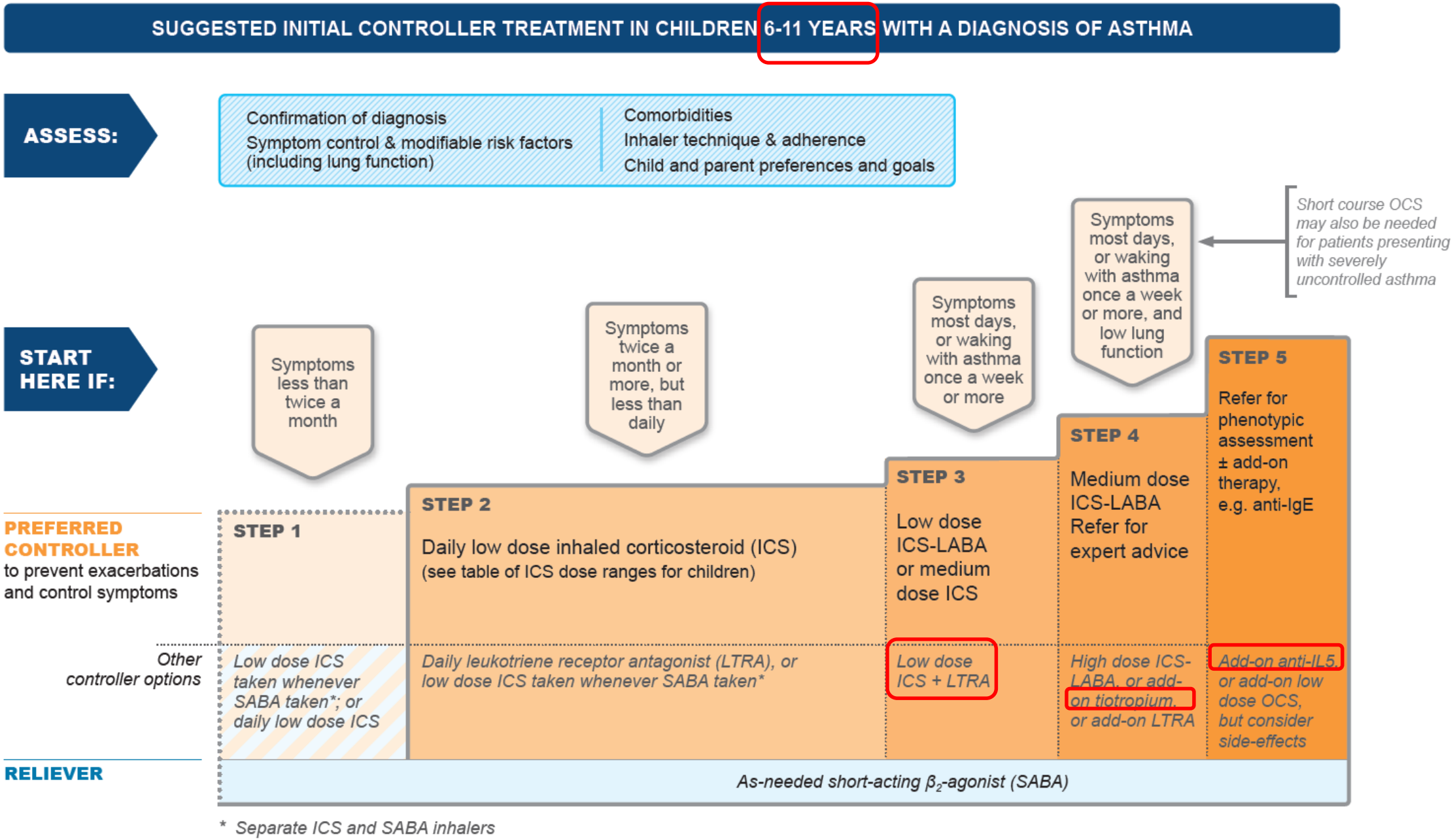
- 藥物治療
- 非藥物治療
- 治療可矯治危險因子

- 症狀
- 急性發作
- 副作用
- 家長 / 監護人滿意度

- 診斷
- 症狀控制及危險因子
- 吸入器的使用技巧以及遵囑性
- 家長 / 監護人偏好

首選控制型藥物	第一階	第二階	第三階	第四階	第五階
考慮給予每天低劑量 ICS		低劑量 ICS	低劑量 ICS / LABA	中 / 高劑量 ICS / LABA	轉介專科醫師進行治療 如： IgE 抗體*
		白三烯素受體拮抗劑（LTRA）*	中/高劑量 ICS或低 ICS + LTRA * #	高劑量% ICS + LTRA *	加低劑量 OCS
	短效乙二型交感神經刺激劑（SABA）		有需要時使用 SABA 或 低劑量 ICS / formoterol		

成人階梯式治療此處為低劑量 ICS / LABA

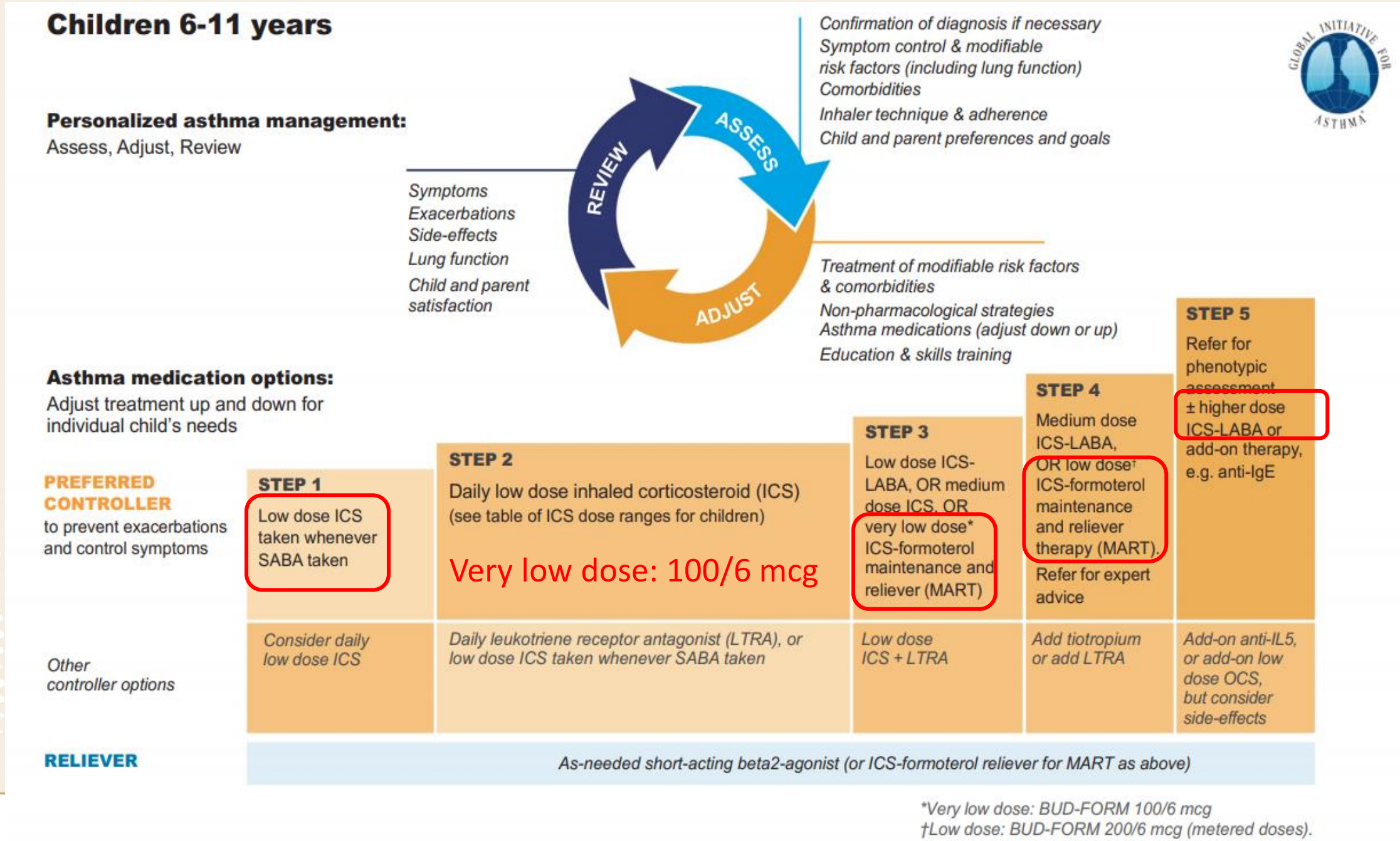


2020 GINA **(Tiotropium : TFDA 核准六歲以上可以使用)**

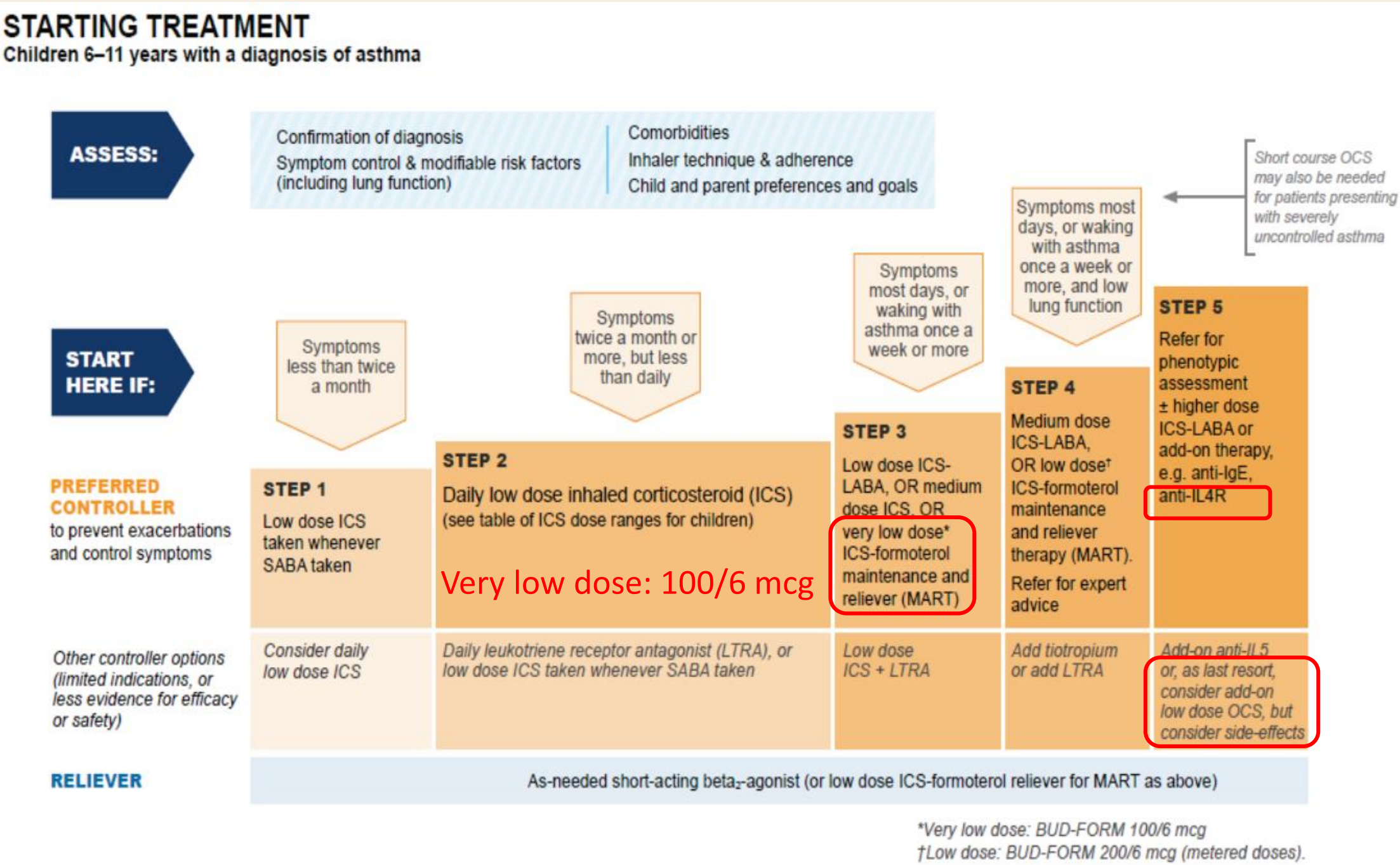
(IL-5 Mepolizumab: TFDA 核准18歲以上)

GINA 2021 (MART : ICS-formoterol in STEP 3,4)

Maintenance and reliever therapy



GINA 2022 (STEP 5 : anti-IL4R)

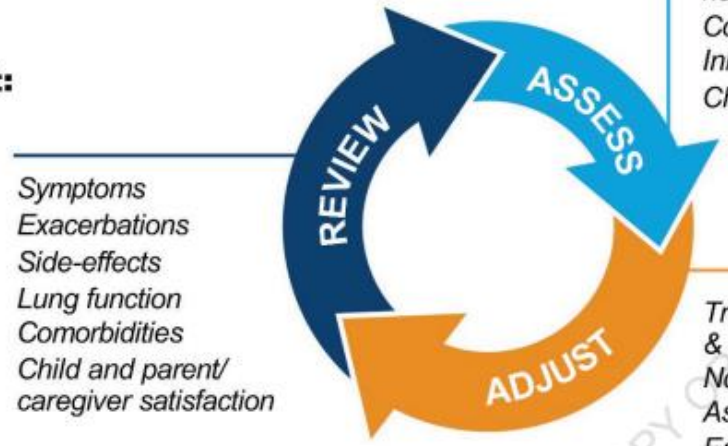


GINA 2023 (STEP 5 : anti-IL5)

Box 8A. The GINA asthma treatment strategy – children 6–11 years

GINA 2023 – Children 6–11 years

Personalized asthma management:
Assess, Adjust, Review



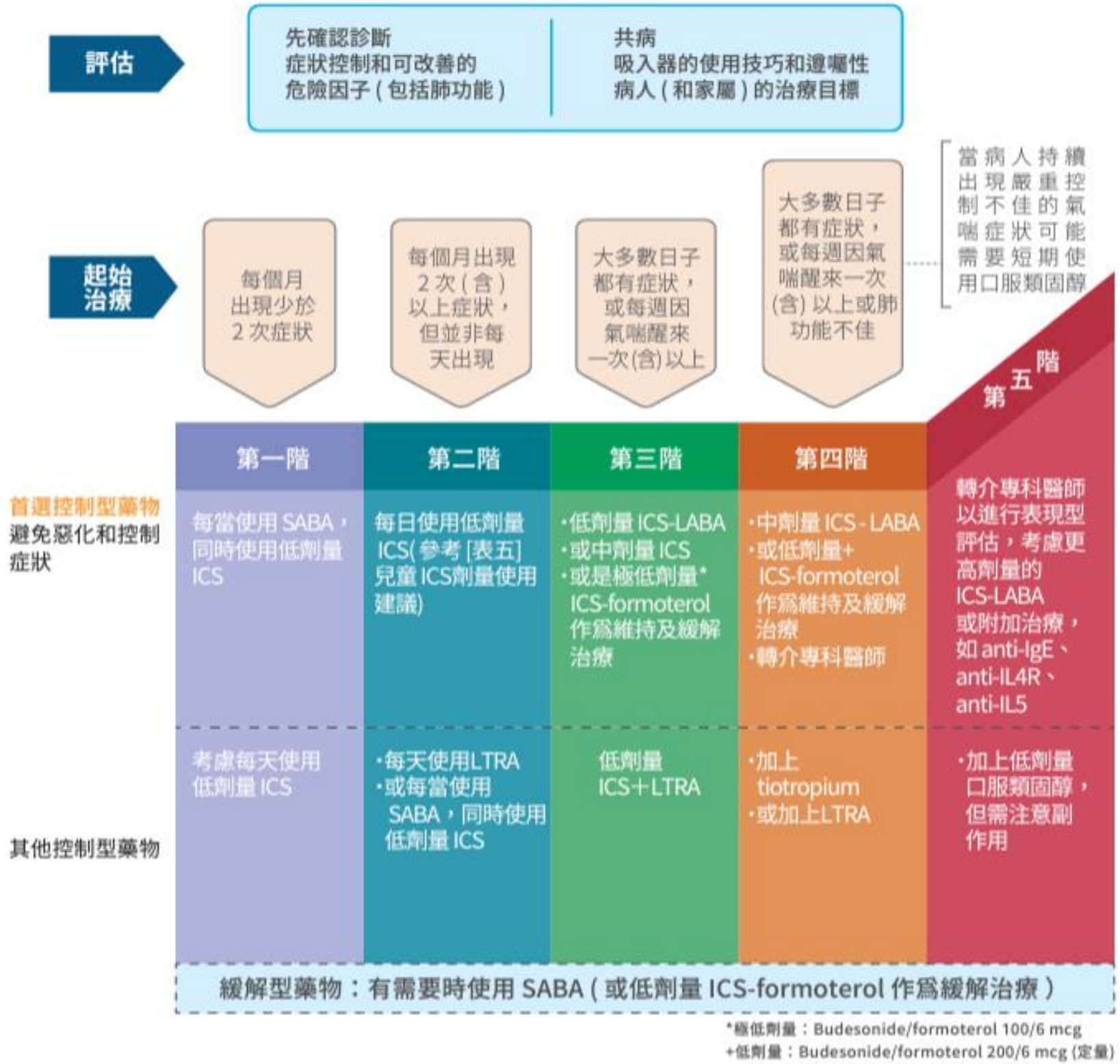
Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 4B)
Comorbidities
Inhaler technique & adherence
Child and parent/caregiver preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Child and parent/ caregiver satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4Rα, anti-IL5
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken**	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*As last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed SABA (or ICS-formoterol reliever* in MART in Steps 3 and 4)				



台灣兒童氣喘診療指引2023

6-11 歲兒童氣喘的治療童第一階

- 首選藥物治療選擇：每當使用 SABA ，一併使用低劑量 ICS
- 規律使用 ICS 加上需要時使用 SABA，對於不常有症狀的兒童，須考慮遵囑性差的問題。

6-11 歲兒童氣喘的治療童第二階

- 首選藥物治療選擇：規律使用低劑量 ICS 加上需要時使用 SABA
- 其他控制型藥物：
  - 每當使用 SABA，一併使用低劑量 ICS
  - 每日使用 LTRA（效力較 ICS 差）

6-11 歲兒童氣喘的治療童第三階

- 首選藥物治療選擇：
  - 將 ICS 增加到中劑量，需要時使用 SABA 作為緩解型藥物
  - 更換使用低劑量 ICS-LABA，需要時使用 SABA 作為緩解型藥物
  - 極低劑量 ICS-formoterol 同時作為控制型及緩解型藥物
- 其他控制型藥物：使用低劑量 ICS 加上 LTRA

6-11 歲兒童氣喘的治療童第四階

- 首選控制型藥物選擇：
  - 中劑量 ICS-LABA
  - 以低劑量 ICS-formoterol 同時作為控制型及緩解型藥物
  - 若氣喘還是控制不佳，轉介給專科醫師，做進一步的評估和建議
- 其他控制型藥物：
  - tiotropium 作為附加治療
  - 若之前沒有使用過 LTRA，可以嘗試加上

6-11 歲兒童氣喘的治療童第五階

- 轉介專科醫師以進行表現型評估並考慮附加治療
- 高劑量 ICS-LABA
- 抗 IgE 單株抗體 omalizumab（嚴重過敏性氣喘的病人）
- 抗 IL-5單株抗體：罹患嚴重嗜酸性白血球增多性氣喘的病人可以使用 anti-IL5單株抗體（皮下 mepolizumab，6 歲以上）
- 抗 IL-4Rα 單株抗體 dupilumab：6 歲以上嗜酸性白血球表現型或口服皮質類固醇依賴型之重度氣喘病人

6-11 歲兒童氣喘的治療童第五階

- 最後考慮加上使用口服類固醇 (≤7.5 mg/day prednisone)：症狀控制不良的病患及排除其他可能因素及其他附加治療後才考慮。需評估及監控類固醇導致腎上腺抑制及骨質疏鬆等風險
- **註：**抗 TSLP 單株抗體 tezepelumab：12 歲以上嚴重氣喘病人，痰液誘導的嗜酸性白血球 (>3%)
- **註：**抗IL5R 單株抗體（皮下 benralizumab，12 歲以上）

各種 ICS 藥物的低、中、高劑量（單位：μg）

ICS	12 歲以上青少年			6-11歲兒童		
	低	中	高	低	中	高
Beclometasone dipropionate (pMDI, 標準顆粒, HFA)	200-500	> 500-1,000	> 1,000	100-200	> 200-400	> 400
Beclometasone dipropionate (12 歲以上：DPI 或 pMDI 極細顆粒, HFA) (6-11 歲：pMDI, 極細顆粒, HFA)	100-200	> 200-400	> 400	50-100	> 100-200	> 200
Budesonide (12 歲以上：DPI 或 pMDI, 標準顆粒, HFA) (6-11 歲：DPI)	200-400	> 400-800	> 800	100-200	> 200-400	> 400
Budesonide (nebules)	n.a.			250-500	> 500-1,000	> 1,000
Ciclesonide (pMDI, 極細顆粒, HFA)	80-160	>160-320	> 320	80	> 80-160	> 160
Fluticasone furoate (DPI)	100		200	50		n.a.
Fluticasone propionate (DPI)	100-250	> 250-500	> 500	50-100	> 100-200	> 200
Fluticasone propionate (pMDI, 標準顆粒, HFA)	100-250	> 250-500	> 500	50-100	> 100-200	> 200
Mometasone furoate (DPI)	取決於 DPI 設備，請參閱藥品仿單			n.a.		
Mometasone furoate (pMDI, 標準顆粒, HFA)	200-400		> 4 00	100		200

* DPI：乾粉吸入器。HFA：氫氟烷烴推進劑。n.a.：not applicable。此表格之內容不代表各藥物之間的臨床等效性 (clinical equivalence)。

台灣兒童氣喘診療指引|2023

2019年後早期使用控制用藥的理由

- 病人三個月內只有輕微氣喘(症狀每週少於一次) [1]
  - 30-37% 成人病患會有急性氣喘發作
  - 16%成人病患有嚴重瀕死的發作
  - 15-20%成人病患死於氣喘
- 誘發因素無法預測(病毒感染,花粉或空污接觸, 藥物遵從性差)

1. Dusser, Allergy 2007

2019年後早期使用控制用藥的理由

- Prevent severe exacerbation which could occur unpredictable !
- 即使一生中只使用 4–5 個療程的口服類固醇仍然會增加骨質疏鬆症，糖尿病，及白內障的風險 [1]
- **規則或頻繁使用支氣管擴張劑噴劑可以造成 β-receptor downregulation, decreased bronchodilator response**

1. Price et al, J Asthma Allerg 2018

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

6-11 歲兒童控制型藥物之治療

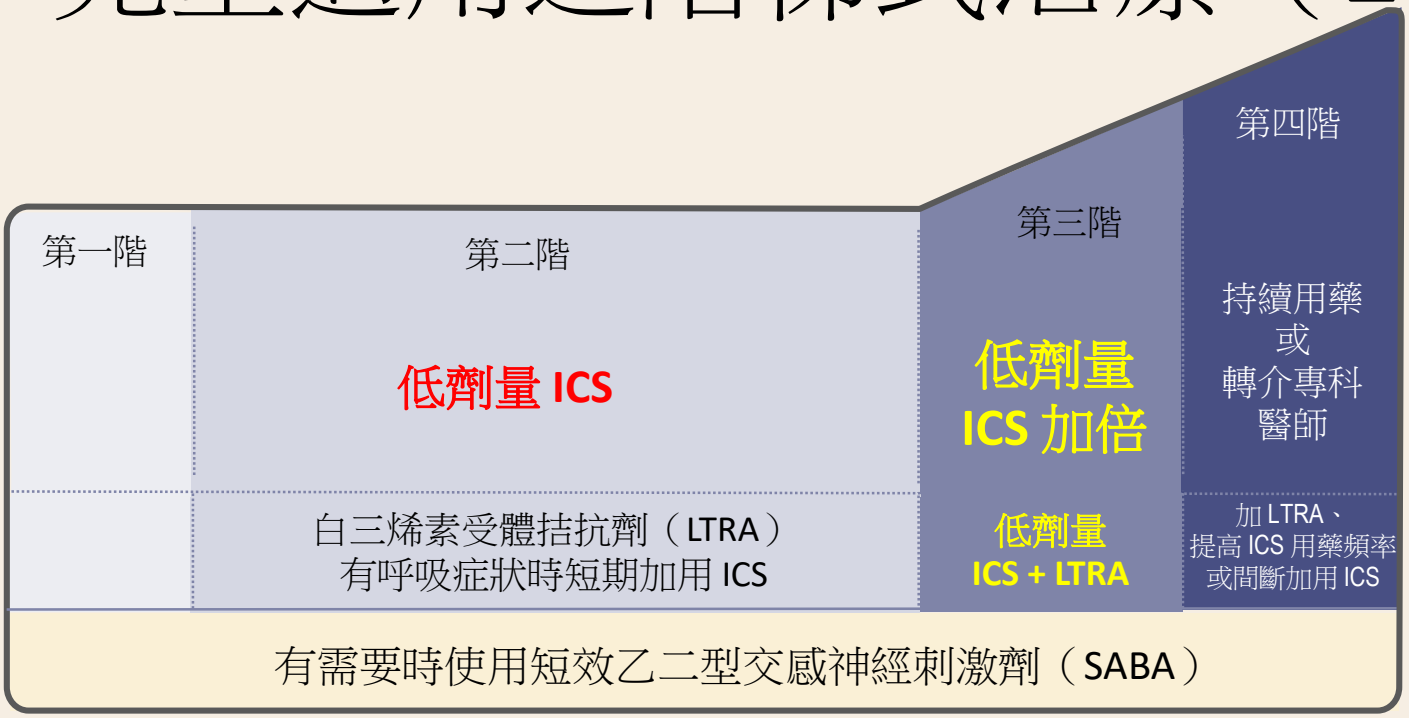
- 早點開始控制型藥物(低劑量 ICS)治療
  - 為有良好預後，氣喘確診後盡早開始控制型藥物之治療 (**幾乎所有病人都可建議**)
- 若有下列情形，考慮升階治療：
  - 多數時候都飽受氣喘症狀困擾
  - 每週因氣喘而從睡眠中清醒 1 次以上，特別是有惡化危險因子之風險族群

6-11 歲兒童控制型藥物之治療

- 若氣喘一開始就有惡化的徵兆：
  - 可給予短期的口服類固醇並定期使用控制型藥物（例如：中 / 高劑量 ICS / LABA 且視情況降階）

- 不建議使用茶鹼theophylline 做控制, 只有微弱的療效但是常有副作用

5 歲以下兒童適用之階梯式治療（2020)



每階兒童治療需納入考量的重點

罕見的病毒性喘鳴及 / 或少量間歇性症狀	• 症狀的模式與氣喘相符且並未良好控制，或每年急性發作 3 次以上 • 症狀模式與氣喘不符但喘鳴頻繁發作（例如間隔 6-8 週就發作） • 給予 3 個月診斷性治療	氣喘確診且已以低劑量 ICS 治療卻仍未良好控制	ICS 加倍仍無法達成良好控制
		需先確認診斷、吸入器使用技巧、用藥遵從性與過敏原暴露情形	

治療重點

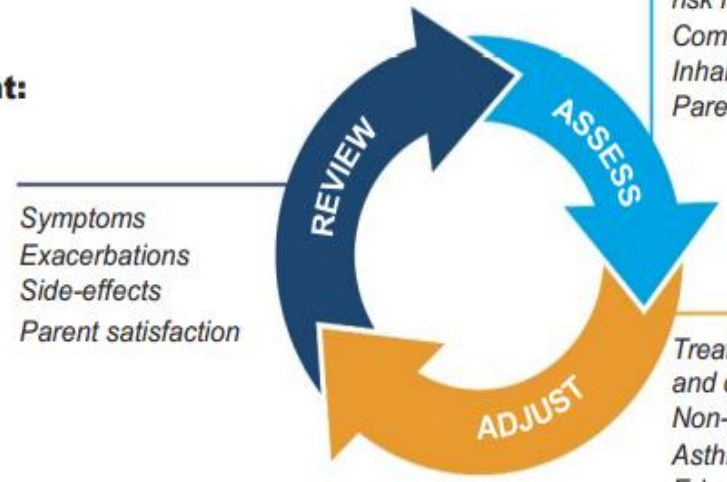
- **評估**症狀控制程度、未來風險與共病
- **自我管理**：衛教、吸入器使用技巧、撰寫氣喘控制計畫與用藥遵從性
- **定期回診**：評估用藥反應、副作用、建立有效治療最小用藥劑量
- 其他有關事宜：環境控制（如：二手煙、過敏原與室內 / 室外空氣污染）

Global Initiative for Asthma. 2020 GINA Report, Global Strategy for Asthma Management and Prevention.

2021 GINA (similar to 2020 GINA)

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Parent preferences and goals

Symptoms
Exacerbations
Side-effects
Parent satisfaction

Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training

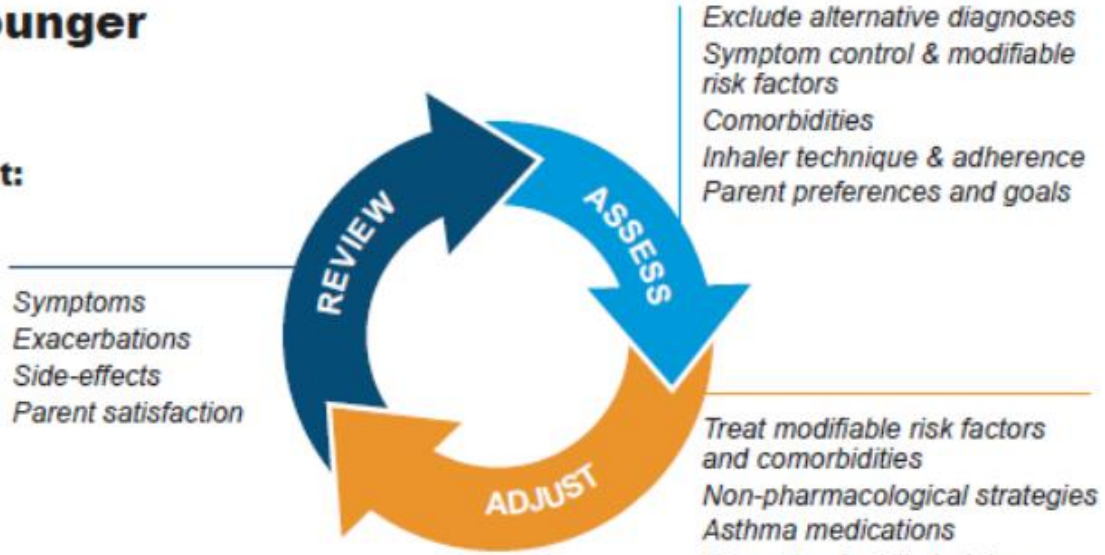
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS	Continue controller & refer for specialist assessment
Other controller options		*Daily leukotriene receptor antagonist (LTRA), or intermittent short courses of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	*As-needed short-acting β_2-agonist*			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS. Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

2022 GINA

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



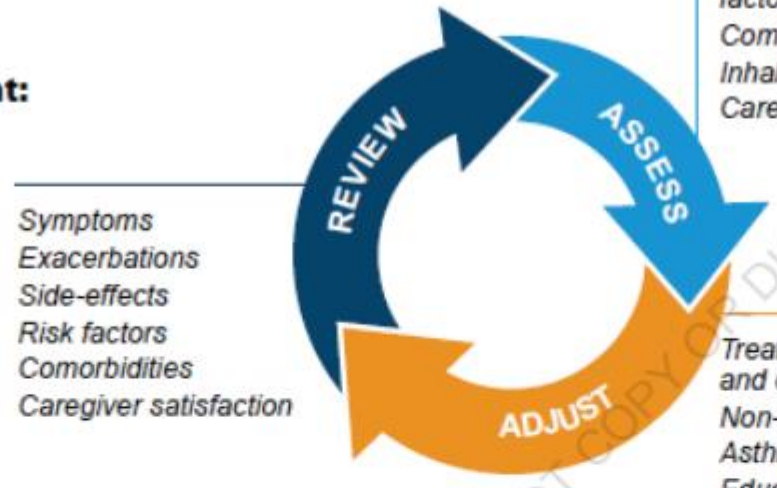
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

2023 GINA

GINA 2023 – Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Caregiver preferences and goals

Symptoms
Exacerbations
Side-effects
Risk factors
Comorbidities
Caregiver satisfaction

Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE	*(Insufficient evidence for daily controller)*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS *(See Box 6-7)*	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

個人化的氣喘處置：評估、調整、檢視反應

- 先確認診斷
- 症狀控制和可改善的危險因子
- 吸入器使用技巧和遵囑性
- 家長的目標

- 治療可改善的危險因子和共病症
- 非藥理策略
- 衛教&操作技巧訓練
- 氣喘藥物

- 症狀
- 惡化
- 副作用
- 家長滿意度

氣喘藥物選擇：依兒童個別需求作升階或降階調整

	第一階	第二階	第三階	第四階
首選控制型藥物之選擇		每日低劑量 ICS	雙倍低劑量 ICS	繼續控制型藥物並轉介給專科醫師
其他控制型藥物	病毒感染誘發氣喘發作時，考慮短期間歇性ICS	・LTRA ・氣喘惡化時使用短期間歇性 ICS	低劑量 ICS＋LTRA，考量轉介專科醫師	・LTRA ・增加 ICS使用頻率 ・加上間歇性 ICS
緩解型藥物：有需要時使用SABA (所有幼兒)				

台灣兒童氣喘診療指引2023

5 歲以下兒童-第一階治療

- 優先選項：視需要使用 SABA, 雖然不是每個病人都有效, 所有喘鳴的病童應該先給予吸入性短效支氣管擴張劑治療 (inhaled SABA) 緩和症狀
- 口服支氣管擴張劑治療 由於較慢作用並且有比較高的副作用, 所以不建議使用

5 歲以下兒童-第一階治療

- 當 SABA 使用率高於一個月每週 2 次時，則需要考慮控制型的藥物。一歲以下兒童的初期喘鳴發作通常都是在感染細支氣管炎的情況下，其需要依細支氣管炎臨床指引做處置，SABA 一般來說對細支氣管炎不具效果

5 歲以下兒童-第一階治療

- 其他選項: 對於有間歇性病毒引發的喘鳴而且平常沒症狀的病童, 尤其是有陽性氣喘預測指標的兒童(API), 當吸入性SABA 仍然效果不佳時, 可以考慮使用間歇性高劑量吸入性類固醇(step 1 in GINA 2022)使用（不過要小心可能的副作用,當醫師確認 ICS 藥物可適當使用時，才可考慮採用）

5 歲以下兒童-第二階治療

- 優先選項：每天規則使用低劑量 ICS 加上視需要使用的 SABA
- 其他選項：持續性氣喘幼童 LTRA 規律治療後，可緩解症狀，並減少口服類固醇的需求。
- 學齡前幼兒Daily ICS 比 LTRA 有效(症狀控制及減少發作)[1]

1. Pediatr Pulmonol 2018;53:1670-7

5 歲以下兒童-第三階治療

- 優先選項：中劑量 ICS（將每日低劑量加倍）
- 其他選項 : 以 LTRA 搭配低劑量 ICS
- ICS+LABA 還沒有足夠資料顯示較佳[1]

1. Pediatr Allergy Immunol 2019; 30:195-203

5 歲以下兒童-第四階治療

- 優先選項：為兒童轉介專科建議和進一步評估(包括氣喘吸入器使用技巧和藥物遵囑性，環境因子控制狀況，重新考量氣喘的診斷）
- 其他選項：
  - **再提高ICS**
  - **若之前沒有使用過 LTRA，可以嘗試加上**
  - **ICS-LABA**
  - **幾週低劑量口服類固醇**
  - **呼吸道感染時短暫使用高劑量ICS**

5 歲以下兒童氣喘的升降階治療

五歲以下兒童用藥調整	
臨床狀況	後續處置
如果是單獨使用中高劑量的吸入型類固醇	應該試圖在 3 個月的期間減少藥量的 50%
吸入型類固醇合併其他藥物治療可獲得控制	先減少 ICS 50% 的劑量，直到達到低劑量之後，再停掉其他控制藥物。
單獨以低劑量的吸入型類固醇就可獲得控制	大多數病患的治療可改成一天一次的劑量
氣喘在使用最低藥量的藥物能獲得控制，且症狀沒有出現**持續一年**	控制藥物治療就可停止

A trial of regular low-dose ICS should be undertaken for children with frequent viral-induced wheezing and with interval asthma symptoms

Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

5 歲以下兒童使用吸入型類固醇的低階每日劑量

ICS	每日總低階劑量 (μg)
Beclometasone dipropionate (pMDI, 標準顆粒, HFA)	100（≧ 5 歲）
Beclometasone dipropionate (pMDI, 極細顆粒, HFA)	50（≧ 5 歲）
Budesonide nebulized	500（≧ 1 歲）
Fluticasone propionate (pMDI, 標準顆粒, HFA)	50（≧ 4 歲）
Fluticasone furoate (DPI)	沒有≦ 5 歲的足夠研究
Mometasone furoate (pMDI, 標準顆粒, HFA)	100（≧ 5 歲）
Ciclesonide (pMDI, 極細顆粒, HFA)	沒有≦ 5 歲的足夠研究

HFA：氟氫烷推噴劑；DPI：乾粉吸入器；pMDI：加壓定量噴霧吸入器。此非臨床等效性列表。
低階每日劑量定義爲：在含有安全性指標的試驗中使用時，未曾發生臨床不良作用的劑量。

台灣兒童氣喘診療指引|2023

氣喘兒童需定期檢測身高

- 至少每年檢測 1 次身高，因為[1]：
  - 控制不佳的氣喘會影響成長
  - 成長速率在開始 ICS 治療的頭兩年會變慢，但並不會持續或惡化[2]
  - 有研究顯示，長期施用 ICS 治療者與常人成年後身高的差異只有 0.7%[3]
  - 100-200 mcg ICS 通常沒有任何對生長的影響
- 若成長速率減緩，應考慮[1]：
  - 氣喘控制不佳
  - 頻繁使用口服類固醇
  - 營養不良

1. Pedersen S, et al. Am J Respir Crit Care Med. 2001;164:521-35; **2.** Kelly HW, et al. N Engl J Med. 2012;367:904-12; **3.** Loke YK, et al. PLoS One. 2015;10:e0133428.

SABA/LABA

- 目前對青少年 (包括成人) 已不建議單獨使用吸入型短效擴張劑，為了獲得最佳的治療結果，在確診病人有氣喘時便應及早給予含有 ICS 的控制型藥物治療
- 過度使用 SABA 在成人、青少年與兒童族群與氣喘急性惡化風險增加具有相關性
- Side effects: tremor, increased nervousness and insomnia in children

LAMA (Long-acting antimuscarinics, tiotropium)

- 台灣適應症(**Tiotropium):** 已接受吸入性皮質類固醇合併其他控制型藥 物仍未控制症狀之 **6** 歲及以上的嚴重持續性氣喘病人，作為維持性支氣管擴張劑附加治療。
- In adults:
  - Improves lung function modestly , but not quality in life
  - In adults: Meta-analysis showed 17% reduction in risk of severe exacerbations
- **Sufficient ICS given** (at least medium dose) before adding LAMA

Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

LAMA (Long-acting antimuscarinics, tiotropium)

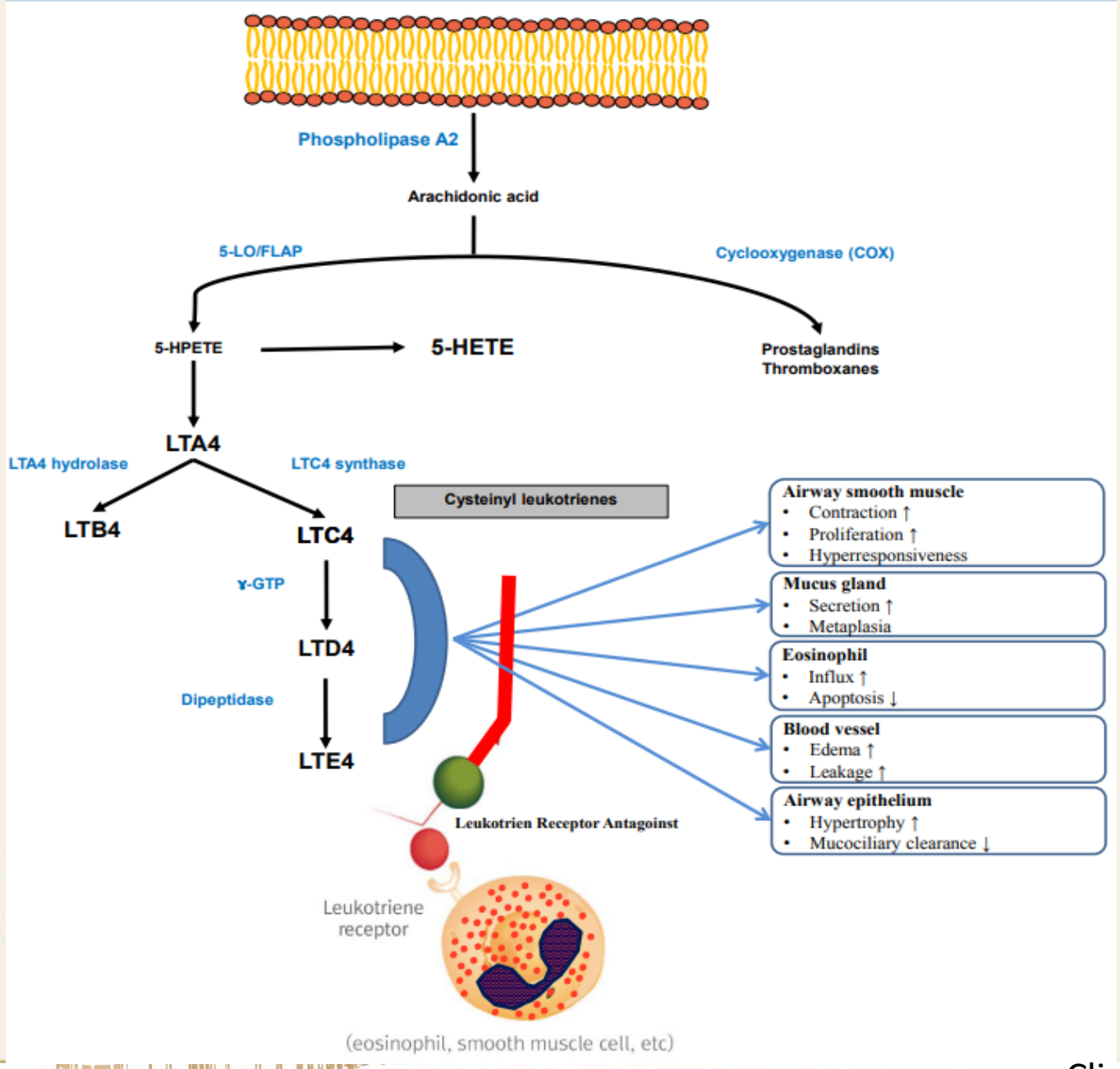
In pediatrics:

- Significant improvement in FEV1, Asthma Control Questionnaire responders
- Reduce the number of patients with one or more exacerbations

Side effect: urinary retention and lower urinary tract symptoms, particularly in elderly males, excessive dry mouth, headache, and dizziness

Pediatric Allergy and Immunology, Volume: 28, Issue: 6, Pages: 573-578, First published: 10 July 2017, DOI: (10.1111/pai.12759)

LTRA(Leukotrine Receptor Antagonist



Leukotrine:

- Powerful lipid mediators of inflammation
- LTB4: chemoattractant for neutrophil and some T-cell
- CysLTs (Cysteinyl leukotrienes): Most powerful bronchocontstrictors known
- **Montelukast**: CysLT receptor antagonist
- Zileuton : 5-LO inhibitor

Clin Exp Pediatr 2020;63(10):376-81

LTRAs versus Placebo

REVIEW

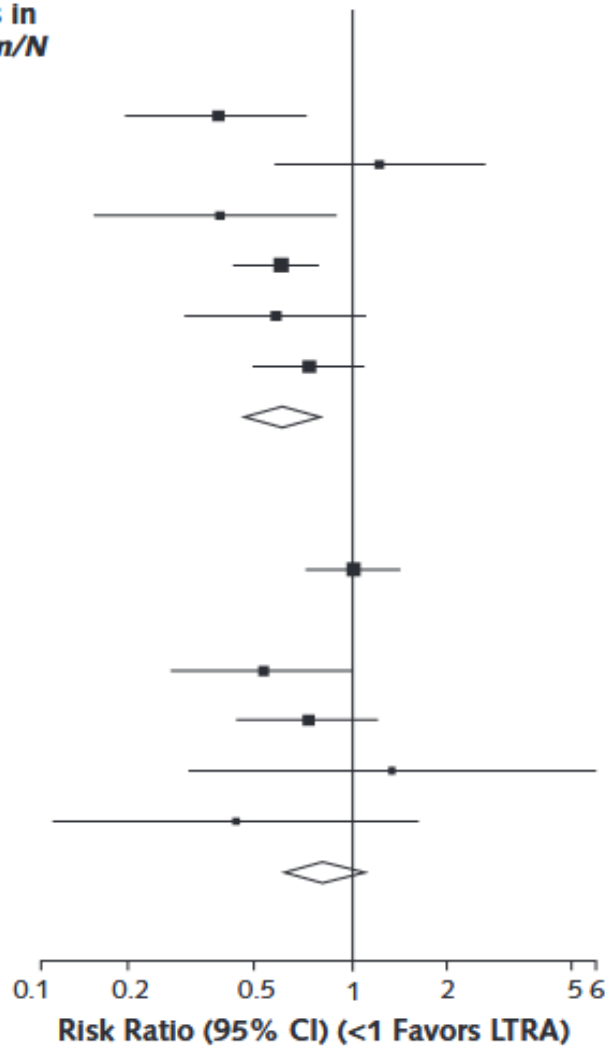
Annals of Internal Medicine

Leukotriene-Receptor Antagonists Versus Placebo in the Treatment of Asthma in Adults and Adolescents

A Systematic Review and Meta-analysis

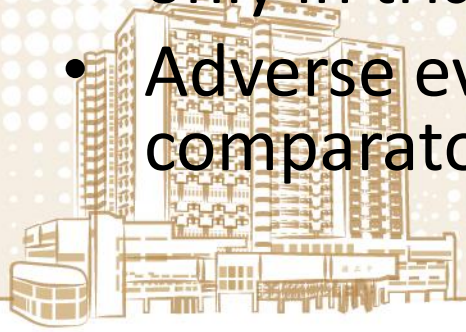
Study, Year (Reference)	Estimated Risk Ratio (95% CI)	Events/Patients in LTRA Group, *n/N*	Events/Patients in Placebo Group, *n/N*
LTRA monotherapy vs. placebo	0.37 (0.19–0.72)	17/308	15/101
Baumgartner et al, 2003 (24)	1.21 (0.57–2.59)	13/111	13/114
Busse et al, 2001 (25)	0.37 (0.15–0.88)	10/337	9/111
Israel et al, 2002 (34)	0.57 (0.42–0.78)	60/382	69/252
Malmstrom et al, 1999 (43)	0.57 (0.29–1.10)	13/231	22/223
Nathan et al, 1998 (46)	0.73 (0.48–1.09)	36/334	48/323
Price et al, 2013 (50)	0.60 (0.44–0.81)	149/1703	174/1124
Subgroup LTRA monotherapy ($I^2 = 34\%$; $P = 0.18$)			
LTRAs plus ICSs vs. placebo plus ICSs	1.01 (0.71–1.42)	47/160	45/154
American Lung Association Asthma Clinical Research Centers, 2007 (20)	0.52 (0.27–1.01)	12/193	24/200
Laviolette et al, 1999 (40)	0.72 (0.43–1.20)	28/408	26/273
Reiss et al, 1998 (52)	1.33 (0.30–5.83)	4/120	3/120
Wise et al, 2009 (65) (A)	0.43 (0.11–1.62)	3/117	7/117
Wise et al, 2	0.80 (0.60–1.07)	94/998	105/864
Subgroup LTRA as add-on therapy ($I^2 = 16\%$; $P = 0.31$)			

Ann Intern Med. 2015;163:756-767.



LTRAs versus Placebo

- Random-effects meta-analyses of 6 trials of LTRA monotherapy showed that LTRAs reduced the risk for an exacerbation (summary risk ratio [RR], 0.60 [95% CI, 0.44to 0.81])
- In 4 trials of LTRAs as add-on therapy to inhaled corticosteroids, the summary RR for exacerbation was 0.80 (CI, 0.60to 1.07)
- Leukotriene-receptor antagonists either as mono-therapy or as add-on therapy to inhaled corticosteroids increased FEV1, whereas FEV1 percentage of predicted values was improved only in trials of LTRA monotherapy
- Adverse event rates were similar in the intervention and comparator groups

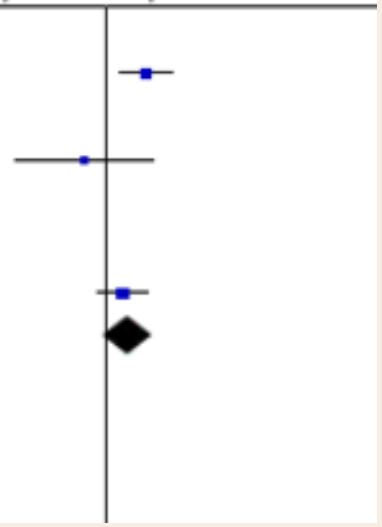


Comparison with ICSs in pediatric patients

Study or Subgroup	Anti-leukotrienes Events	Total	Inhaled steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Paediatrics						
Garcia Garcia 2005	86	495	51	495	14.8%	1.69 [1.22, 2.33]
Kumar 2007	0	30	0	32		Not estimable
Maspero 2001	11	83	7	41	6.0%	0.78 [0.32, 1.85]
Stelmach 2002a	0	18	0	19		Not estimable
Stelmach 2002b	0	27	0	28		Not estimable
Szefler 2007	63	197	50	197	14.9%	1.26 [0.92, 1.73]
Subtotal (95% CI)		**850**		**812**	**35.7%**	**1.35 [0.99, 1.86]**
Total events	160		108			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.48$, df = 2 (P = 0.18); $I^2 = 43\%$

Test for overall effect: Z = 1.87 (P = 0.06)



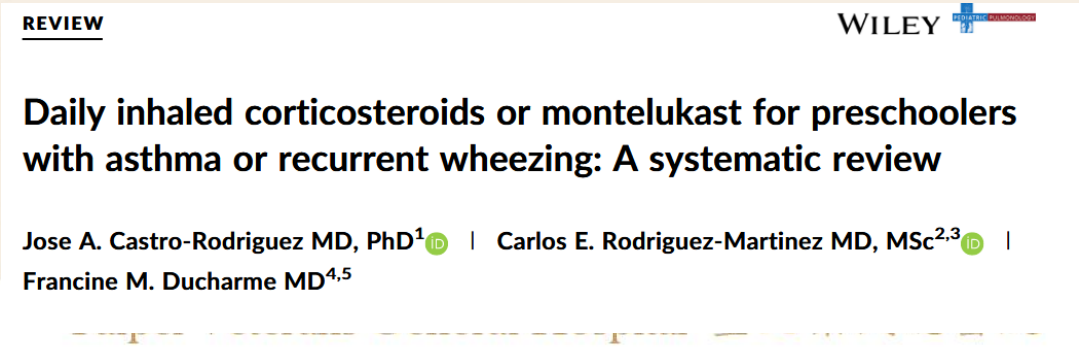
A Cochrane review that analyzed 19 pediatric randomized controlled trials (RCTs) to compare the efficacy of montelukast to that of ICS revealed the superior efficacy of ICS

Cochrane Database Syst Rev 2012;(5): CD002314

Comparison with ICS for preschoolers

- Narrative synthesis of 29 randomized, prospective, controlled trials
- Based on trials at lowest risk of bias and the largest open-labelled studies, ICS was associated with better control of symptoms and less exacerbations than LTRA. And also less need for rescue SC
- Insufficient data of high quality prevented firm conclusions on other secondary outcomes (unscheduled visits to ED, rescue systemic corticosteroids, improvement of lung function, adverse events)

Pediatr Pulmonol 2018;53: 1670-7


REVIEW

WILEY

Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: A systematic review

Jose A. Castro-Rodriguez MD, PhD[1] | Carlos E. Rodriguez-Martinez MD, MSc[2,3] | Francine M. Ducharme MD[4,5]

LTAs versus ICS in “real world”

- Adherence to montelukast was superior to ICS
  - Similar real-world efficacies in the treatment of children with mild asthma

Ann Allergy Asthma Immunol. 2003;90(5):543

Controller therapy in Asians and whites with persistent Asthma

- Retrospective study in U.S. in non-Hispanic White and Asian patients with persistent asthma
- Compared with low-dose ICS monotherapy, montelukast monotherapy evidenced a lower incidence rate (RR 0.89, p=0.03) but similar hazard rate (HR 0.96, p=0.43) of asthma exacerbation in white patients 12 years of age or older
- No difference observed in Asian patients or in white children 4-11 years of age
- No difference observed in children in all other comparisons:
  - Montelukast + low-dose ICS vs. LABA+ low dose ICS
  - Montelukast + low-dose ICS vs. medium-dose ICS
  - Montelukast + medium-dose ICS vs. LABA+ medium-dose ICS

Asian Pac J Allergy Immunol 2019; 37(2):73-86

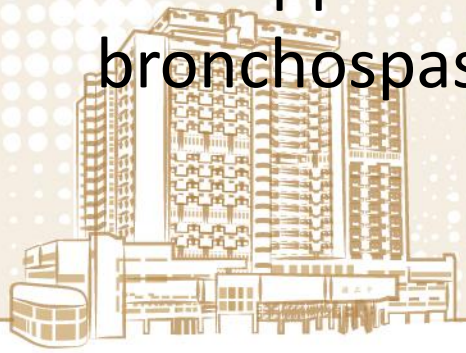
LTAs in exercise-induced bronchospasm

- Protection against EIB as early as 2 hours after a single oral dose & persisting up to 24 hours [1]
- US FDA approved for this indication
- Sustainable effects to inhibit EIB after 4-8 weeks of montelukast, compared waning protection with salmeterol [2]

1. Ann Allergy Asthma Immunol. 2006;97(1):98
2. Chest. 2005;127(5):1572

The role of Montelukast in allergic diseases

- An alternative treatment of asthma when maintenance therapy is needed
- An add-on treatment to existing low-dose inhaled corticosteroid in asthma patients
- However, in the real-world setting, many doctors and patients prefer montelukast over ICSs despite their lower efficacy. And due to better adherence, similar real-world efficacies was noted in the treatment of children with mild asthma
- FDA approved indication for prevention of exercise-induced bronchospasm



Montelukast

Box warning of Singulair® : Data summary

- Observational study from *FDA's Sentinel System* (2010-15)
  - The risk of **inpatient depressive** disorder associated with montelukast use compared to ICS was **not** significant (overall HR: 1.06; 95% CI: 0.90-1.24)
  - Exposure to montelukast was also **not** associated with self-harm (HR:0.92; 95% CI: 0.69-1.21) or modified self-harm (HR: 0.81; 95% CI: 0.63-1.05)
  - Exposure to montelukast was significantly associated with a **decreased** risk of treated **outpatient** depressive disorder (overall hazard ratio [HR]: 0.91; 95% confidence interval [CI]: 0.89-0.93)

Montelukast

Box warning of Singulair® : Data summary

- Animal study review [1]
  - Orally administered montelukast (10 mg/kg/day for 7 days) was detectable in brain tissue and cerebrospinal fluid in rats
  - This finding providing evidence of its ability to cross the blood-brain barrier

1. Marschallinger J et al. Nat Commun 2015;6:8466

Box warning of Singulair® : Data summary

- Reporting trend evaluation
  - Finding：There was an increase in reporting of neuropsychiatric events around the time of the initial communications from FDA in 2008 (*FDA communication 2008*)

Box warning of Singulair® : Data summary

- Focused evaluation of completed suicides cases (82) (*FDA website: Data summary*)
  - Finding： Most cases (48) did **not** contain sufficient key information
  - In the remaining 34 cases better documented, many of them have additional risk factors that may have contributed to the suicide

Open access Original research

BMJ Paediatrics Open

Adverse drug reactions of leukotriene receptor antagonists in children with asthma: a systematic review

Eleanor Grace Dixon ,[1,2] Charlotte EM Rugg-Gunn ,[2,3] Vanessa Sellick,[4] Ian P Sinha,[2,5] Daniel B Hawcutt[2,6]

- Embase, MEDLINE, PubMed and CINAHL till Oct 2020
- 15 Eligible studies: 1 RCT, 7 cohort/ case-control, 7 case reports
- 6853 patients received LTRA
- 1050 patients in RCT, prospective studies

BMJ Paediatrics Open 2021;5:e001206. doi:10.1136/bmjpo-2021-001206

Results

- 48 ADRs in total in 13 organ systems; 20 ADRs were psychiatric disorders (in 10 of 15 studies)
- Anxiety, sleep disorder(e.g., sleep terror), mood disorders(agitation/hyperactivity) were the most common ADRs across all studies (15 studies)

Discussions:

- LTRAs can induce ADRs at any point after using drugs
- Step down treatment when asthma is stable

Box warning of Singulair® :

- Further research is still needed to clarify the association between montelukast and NE (Neuropsychiatric event)
- Advise patients and parents/caregivers that the patient should stop taking montelukast and contact a health care professional immediately if any NE occur
- Monitor all patients treated with montelukast for neuropsychiatric symptoms.

CONTENT

生物製劑

Biologics in severe asthma: A pragmatic approach for choosing the right treatment for the right patient

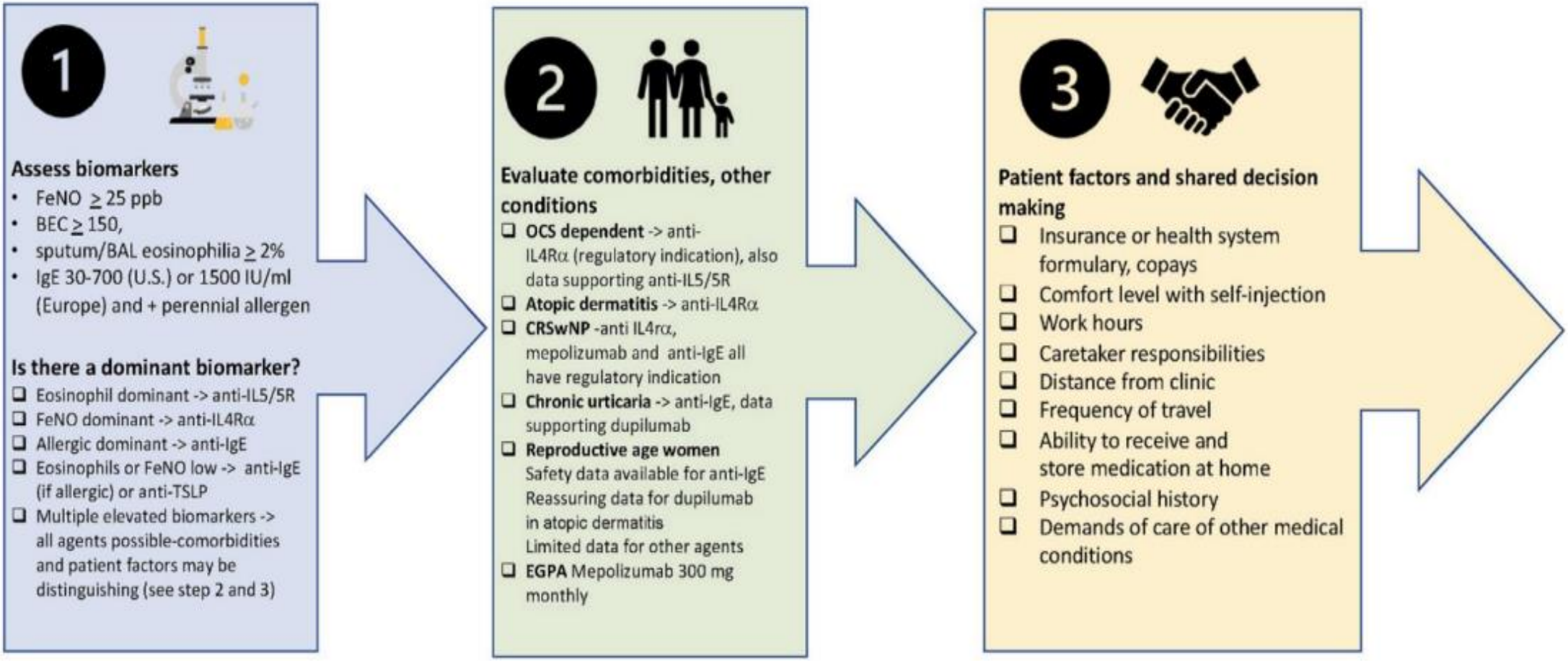


Fig. 2. A pragmatic approach to choosing an asthma Biologic.

Respiratory Medicine 218 (2023) 107414

Clinical phenotype

- T2-high asthma (BEC, FeNO, IgE elevated)
  - Early-onset allergic asthma
  - Late-onset nonallergic asthma
  - Aspirin-exacerbated respiratory disease (AERD)
- T2-low asthma (The T1 and T3 immune pathways play main roles: T3 (mediated by Th17 lymphocytes and ILC3)
  - Smoking asthma
  - Obesity-induced asthma
  - Asthma in the elderly
  - Post-menopausal asthma

Eur Respir Rev 2023; 32: 220201

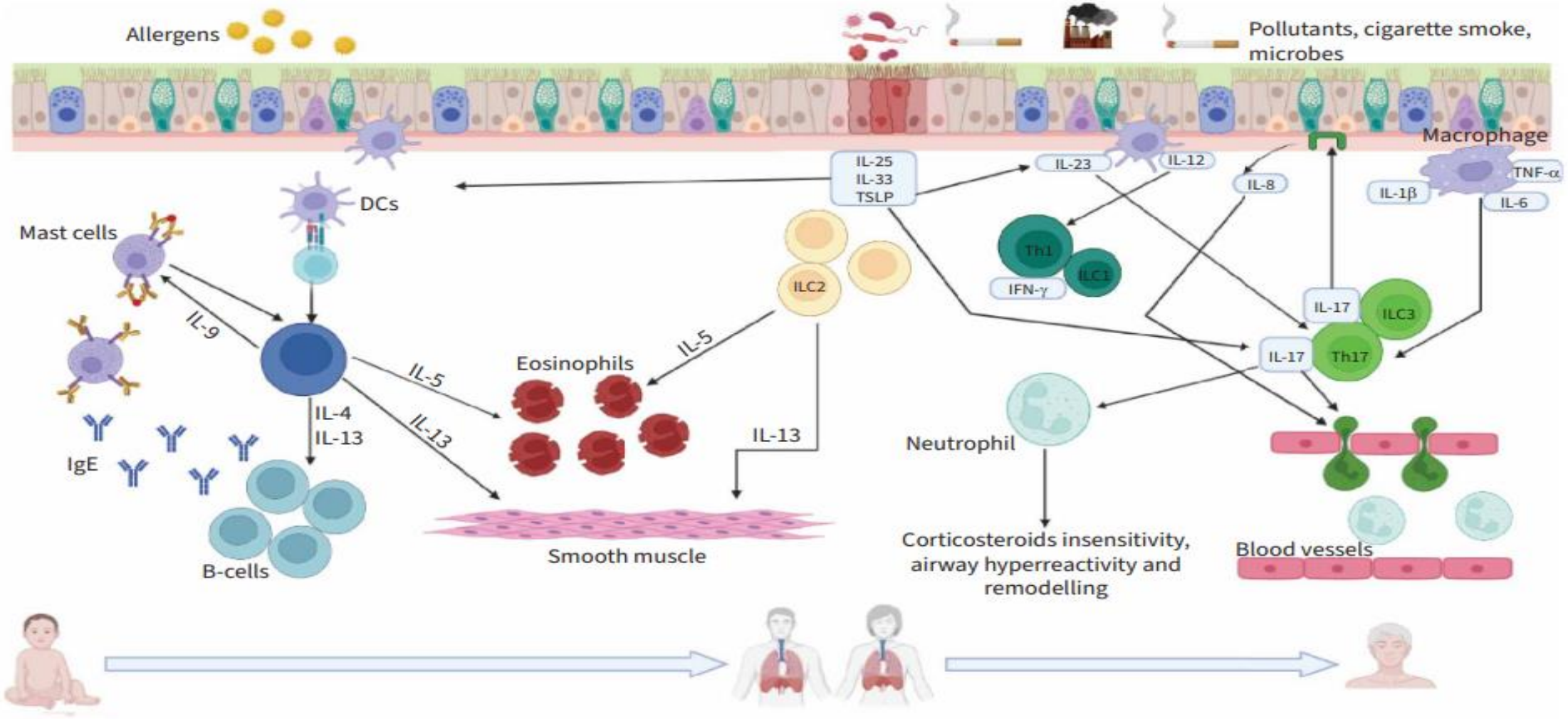


FIGURE 2 Schematic representation of the T2-high and T2-low pathways occurring during the course of life upon exposure to different stimuli. T2-high: after injury, epithelial cells release alarmins (interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP)) that activate innate lymphoid cells (ILCs) and dendritic cells (DCs). Upon allergen/antigen uptake, processing and presentation to naïve T-cells, DCs promote the differentiation of naïve T-helper (Th) cells into Th2 lymphocytes. ILC2 and Th2 secrete pro-inflammatory cytokines, exerting key roles in T2 immune response. T2-low: allergens, pollutants, cigarette smoke, viruses and bacteria can damage and stimulate the airway epithelium, which releases TSLP, IL-33, IL-25 and chemokines such as IL-8 acting as neutrophil chemoattractants. Macrophages and DCs elicit the recruitment of neutrophils and the release of pro-inflammatory cytokines by Th17/ILC3 and Th1/ILC1 cells. IFN-γ: interferon-γ; TNF-α: tumour necrosis factor α. Created in BioRender.com.

Anti-IgE (Omalizumab)

- First biologic therapy for severe asthma approved in 2003
- Binding to Fc-Fragment of free IgE, blocking the activation of mast cells and other IgE-mediated pathway
- Had proven effect in moderate-to-severe and severe persistent IgE-mediated asthma
- Randomized controlled study in 6-11 yrs children showed significant reduced urgent unscheduled physician visits by 30%

- Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

Anti-IgE (Omalizumab)

- Significant improvement in quality of life both during stable ICS dosing and during tapering in anti-IgE group
- **Restoration virus-induced IFN-α responses** → preventative effects on respiratory virus–associated exacerbations [1]

- Further approved for chronic spontaneous urticaria(CSU) and CRSwNP (Chronic rhinosinusitis with nasal polyps)
- 台灣健保規範: IgE 介於 30-1300 IU/mL 的**6歲以上**嚴重氣喘患者，依照患者之 IgE 總量與體重決定施打劑量

- Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.
- 1. J Allergy Clin Immunol 2015;136:1476-85

Anti-IgE (Omalizumab)

- Side effect:
  - Not different from placebo in several trials [1,2,3]
  - Severe anaphylaxis has been occasionally described [4]
  - No increase in the rate of major birth defects or miscarriage was observed in a prospective pregnancy registry [5]

1. Journal Allergy Clinical Immunol. 108(2), 184-90
2. Allergy 60(3), 309-316
3. European Respiratory Journal 18(2):, 254-61
4. FDA
5. Journal Allery Clinical Immunol. 135(2),407-12

IgE 基值 (IU/ml)	體重 (公斤)									
	≥ 20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥ 30-100	75	75	75	150	150	150	150	150	300	300
>100-200	150	150	150	300	300	300	300	300	450	600
>200-300	150	150	225	300	300	450	450	450	600	375
>300-400	225	225	300	450	450	450	600	600	450	525
>400-500	225	300	450	450	600	600	375	375	525	600
>500-600	300	300	450	600	600	375	450	450	600	
>600-700	300	225	450	600	375	450	450	525		
>700-800	225	225	300	375	450	450	525	600		
>800-900	225	225	300	375	450	525	600			
>900-1000	225	300	375	450	525	600				
>1000-1100	225	300	375	450	600					
>1100-1200	300	300	450	525	600					
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

每四週投藥一次
每兩週投藥一次
□不可給藥 - 無建議劑量的資料

Anti-IL-5 (Mepolizumab)

- Approved in Europe for children 6 years and older with severe eosinophilic asthma (BEC >150/ul) [1]
- Efficacy data in this population are limited to one very small open label uncontrolled study
- Adults: Strong reduction of OCS dosage while more than 30% patients able to discontinue OCS; reduction in exacerbation more than 50% [2]
- Approved for CRSwNP, EGPA (eosinophilic granulomatosis with polyangiitis), HES (Hypereosinophilc syndrome)

- BEC: Blood Eosinophil Counts; OCS: oral corticosteroid

1. Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.
2. The Journal of Allergy and Clinical Immunology. In Practice 10(10), 2646–2656.
3. Pharmacology & Therapeutics 2023(252),108551

Anti-IL-5 (Mepolizumab)

- Neutralize circulating IL-5 with a reduction in eosinophilic airway inflammation→ Less acute exacerbation [1]
- 台灣核准年齡為 **12歲**以上嗜酸性白血球表現型嚴重氣喘 病患，每四週固定皮下注射 **100 mg** 劑量
- Side effects: well tolerated

1. Drugs 2017; 77(16):1769-1787

Anti-IL4R (Dupilumab)

- Target alpha subunit of the IL-4 receptor, which is necessary for both IL-4 and IL-13 signaling → impairs B-cell activation and prevents eosinophil infiltration into the lung and other tissue [1]
- Approved for > 6 years old with severe asthma
- Blood eosinophils ≥150 and ≤1500/μl, or FeNO ≥25 ppb [2]
- Other approved indication: CRSwNP, atopic dermatitis, prurigo nodularis, eosinophilic esophagitis (EoE) [2]

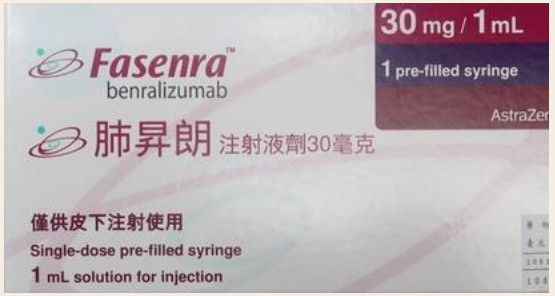
1. Allergy 75(5), 1188–1204
2. Pharmacology & Therapeutics 2023(252),108551

Anti-IL4R (Dupilumab)

- Reduced severe exacerbation rate by 41% and increased lung function by 5.2 percentage points [1]
- Side effect: injection site reactions, transient hypereosinophilia in 14% patient , eosinophilic pneumonia (rare), conjunctivitis, arthralgia [2]
- 台灣核准年齡為 **12 歲**以上嗜酸性白血球表現型的嚴重氣喘病患，用藥前**12**個月內的血中嗜酸性白血球 **≧300 cells/mcL**

1. N Engl J Med 2021; 385: 2230-2240
2. Pharmacology & Therapeutics 2023(252),108551

Anti-IL5Rα : Benralizumab



- Bind to alpha-subunit of IL-5 receptor → depletion of eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity(ADCC) [1]
- Approved for >12 years severe asthma [2]
- Real-life studies found great lung function improvement with FEV1 increases from 300 to 600 ml [3], reduction in OCS-dependent patient [4]

1. The Journal of Allergy and Clinical Immunology 125(6), 1344–1353.e2
2. FDA
3. Journal of Allergy and Clinical Immunology. In Practice 10(12), 3174–3183
4. Chest 159 (2), 496–506.

Anti-IL5Rα : Benralizumab

- 台灣健保核准年齡為 **18歲**以上嗜酸性白血球表現型嚴重氣喘 病患
- Side effect: headache, pharyngitis [1]

1. Pharmacology & Therapeutics 2023(252),108551

Anti-TSLP (**T**hymic **S**tromal **L**ympho**P**oetin) : Tezepelumab

- Block TSLP(胸腺基質淋巴生成素) which mainly activates T2 inflammation via Th2 ND innate pathways. Some studies indicated effects are independent of T2 pathways acting via mast cells on fibrocytes and airway smooth muscle [1]
- Approved for > 12 years old severe asthma [2]
- 台灣健保核准年齡為 **18歲**以上嚴重氣喘 病患

1. The Journal of Clinical Investigation 2019, 129(4): 1141-51
2. FDA

Anti-TSLP (**T**hymic **S**tromal **L**ympho**P**oetin) : Tezepelumab

- Phase 3 Navigator trial showed significant reduction in exacerbations, rapid increase in FEV1, rapid reductions in T2 biomarkers BEC, FeNO, IgE [1]
- Side effects: in long-term extension study: (DESTINATION): 4 cases with severe cardiovascular events – further observation in post-market necessary [2]

1. NEJM 2021: 384(19),1800-9
2. Lancet Respiratory Medicine 2023: 11(5),425-38

Eligibility

Predictors of asthma response

Anti-IgE *(omalizumab)*

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

no / *no*

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*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 ++

no / *no*

Anti-IL4R *(dupilumab)*

*Is the patient eligible for **anti-IL4R** for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

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

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

no / *no*

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

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

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

Eligible for none? Return to section **7**

Key changes to GINA severe asthma guide in 2022 (continued)

- Anti-IL4R* (dupilumab) for severe eosinophilic/Type 2 asthma
  - Not suggested if blood eosinophils (current or historic) >1500/µl
  - Dupilumab now also approved for children ≥6 years with severe eosinophilic/Type 2 asthma, not on maintenance OCS *(Bacharier, NEJMed 2021)*
- Anti-TSLP* (tezepelumab) now approved for severe asthma (age ≥12 years)
  - Greater clinical benefit with higher blood eosinophils and/or higher FeNO
  - Insufficient evidence in patients taking maintenance OCS

Class	Name	Age*	Asthma indication*	Other indications*
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5 Anti-IL5R	Mepolizumab (SC) Reslizumab (IV) Benralizumab (SC)	≥6 years ≥18 years ≥12 years	Severe eosinophilic/Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypereosinophilic syndrome
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/Type 2 asthma, or maintenance OCS	Moderate-severe atopic dermatitis, CRSwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	Severe asthma	

**Check local eligibility criteria for specific biologic therapies; TSLP: thymic stromal lymphopoietin*

CONTENT

急性惡化的處置

5 歲以下兒童 急性氣喘發作的評估

症狀	輕度	重度*
意識改變	無	情緒焦躁、意識混亂或昏睡
室氧飽和度 **	>95%	<92%
說話†	可完整說出句子	僅能說出隻字片語
呼吸速率	<40/min	>40/min
脈搏	<100 bpm	>180 bpm（0–3 歲） >150 bpm（4–5 歲）
發紺	未出現	容易發生
喘鳴強度	多變性	可能聽不到呼吸音

*出現任一症狀及為重度惡化

**氧氣或支氣管擴張劑治療前的血氧飽和度

† 考量兒童的正常發展速度

Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

5 歲以下兒童急性發作處置 (續)

輕度或中度

開始治療

- 每 20 分鐘給予一次 2 puffs 的 salbutamol 100 mcg（以 pMDI + 吸入輔助器給予）或 2.5 mg（以液態吸入劑給予），持續一小時
- 給予氧氣治療（若可取得相關設備）：控制室氧飽和度 94-98%

密切觀察 1-2 小時

若出現下列症狀轉送至加護病房：

- 經 salbutamol 治療 1-2 小時候仍無治療反應
- 任何嚴重惡化的徵兆
- 呼吸頻率加快
- 室氧飽和度下降

惡化或症狀未改善

重度或危及性命

出現緊急狀況

轉送至加護病房

轉送時的等待期間：

- 每 20 分鐘給予一次 6 puffs 的 salbutamol 100 mcg（以 pMDI + 吸入輔助器給予）或 2.5 mg（以霧化劑給予）
- 給予氧氣治療（若可取得相關設備）：控制室氧飽和度 94-98%
- 給予 prednisolone 起始劑量 2 mg/kg（<2 歲者最高劑量 20 mg；2-5 歲者最高劑量 30 mg）
- 每 20 分鐘給予一次 ipratropium bromide 160 mcg（或以霧化劑給予 250 mcg）持續一小時

Global Strategy for Asthma Management and Prevention 2023. Global Initiative for Asthma (GINA).

5 歲以下兒童的急性氣喘處置後的追蹤

出院與追蹤計畫

- 確保家中有適當可用應急資源
- 必要時持續使用緩解型藥物
- 考慮吸入器的使用
- 衛教吸入器的用法與使用頻率
- 一週內持續追蹤
- 提供並解釋治療計畫

後續追蹤

- **緩解型藥物**：評估後可改為有需要時才使用
- **控制型藥物**：依據病人發生惡化的原因，持續給予病人短期（1-2 週）或長期（3 個月）的高劑量控制型藥物治療
- **危險因子**：檢查病人是否具有可修正的惡化危險因子並加以改善，包括吸入器的操作技巧、遵囑性等
- **治療計畫**：病人是否了解？操作上是否適當？是否需要調整？

CONTENT

兒童氣喘的日常預防建議

氣喘的初級預防

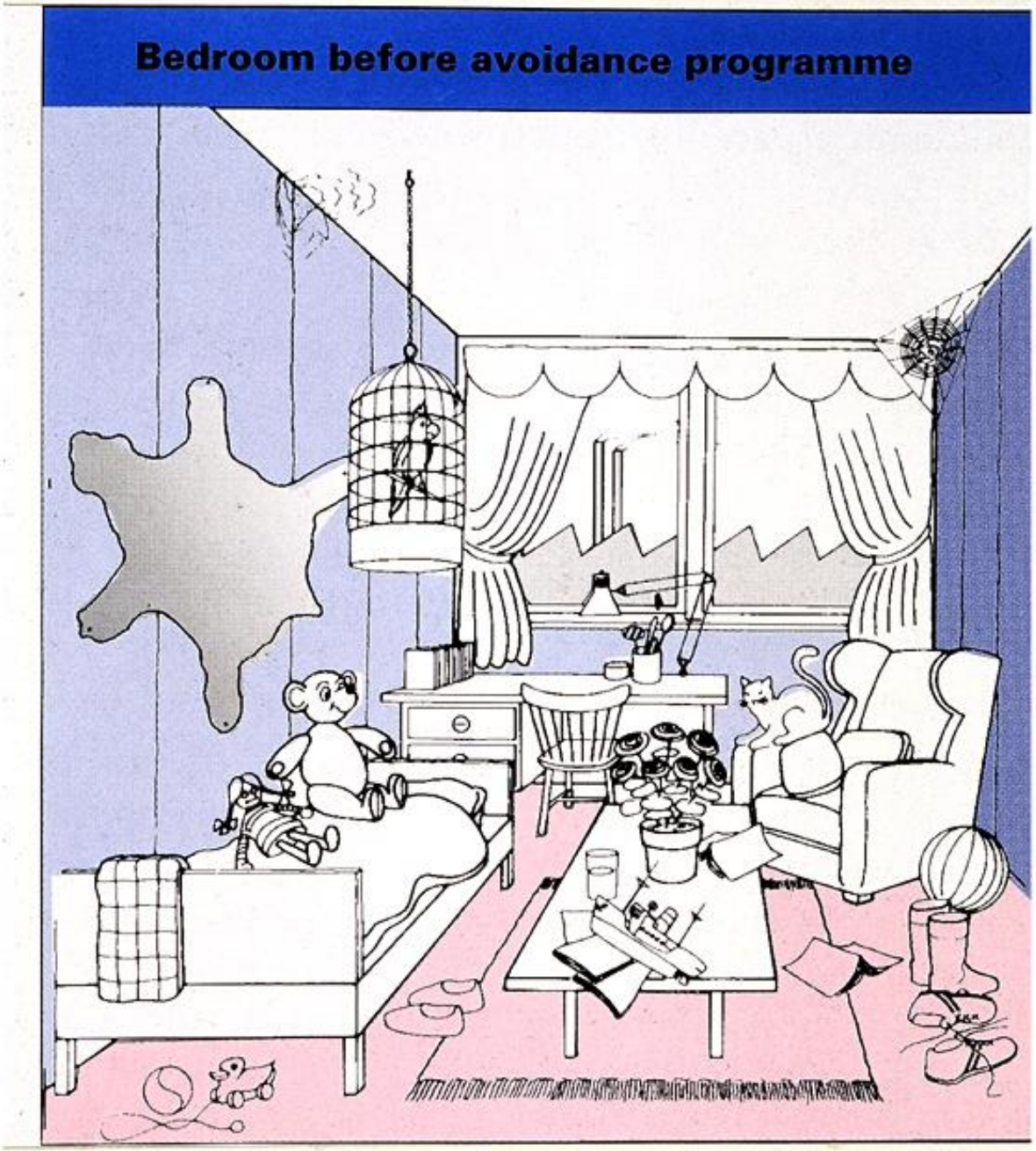
- 基因與環境的交互作用是造成氣喘發展與持續的成因
- 對兒童而言，胎兒時期與新生兒階段是關鍵，但仍有待進一步研究
- 處置策略包含避開過敏原
  - 僅針對單一過敏原的策略通常不夠有效
  - 多方考量的策略或可發揮作用，但卻無法得知關鍵過敏原
- **現行建議**
  - **懷孕與新生兒時期避免接觸二手菸**
  - **懷孕中的母親(或計畫懷孕)如有維生素D缺乏，應予矯正，可減少出生後嬰幼兒的喘鳴**
  - **鼓勵自然產**
  - **為整體健康考量，鼓勵母乳哺育**
  - **新生兒 1 歲前盡可能避免使用廣效抗生素**

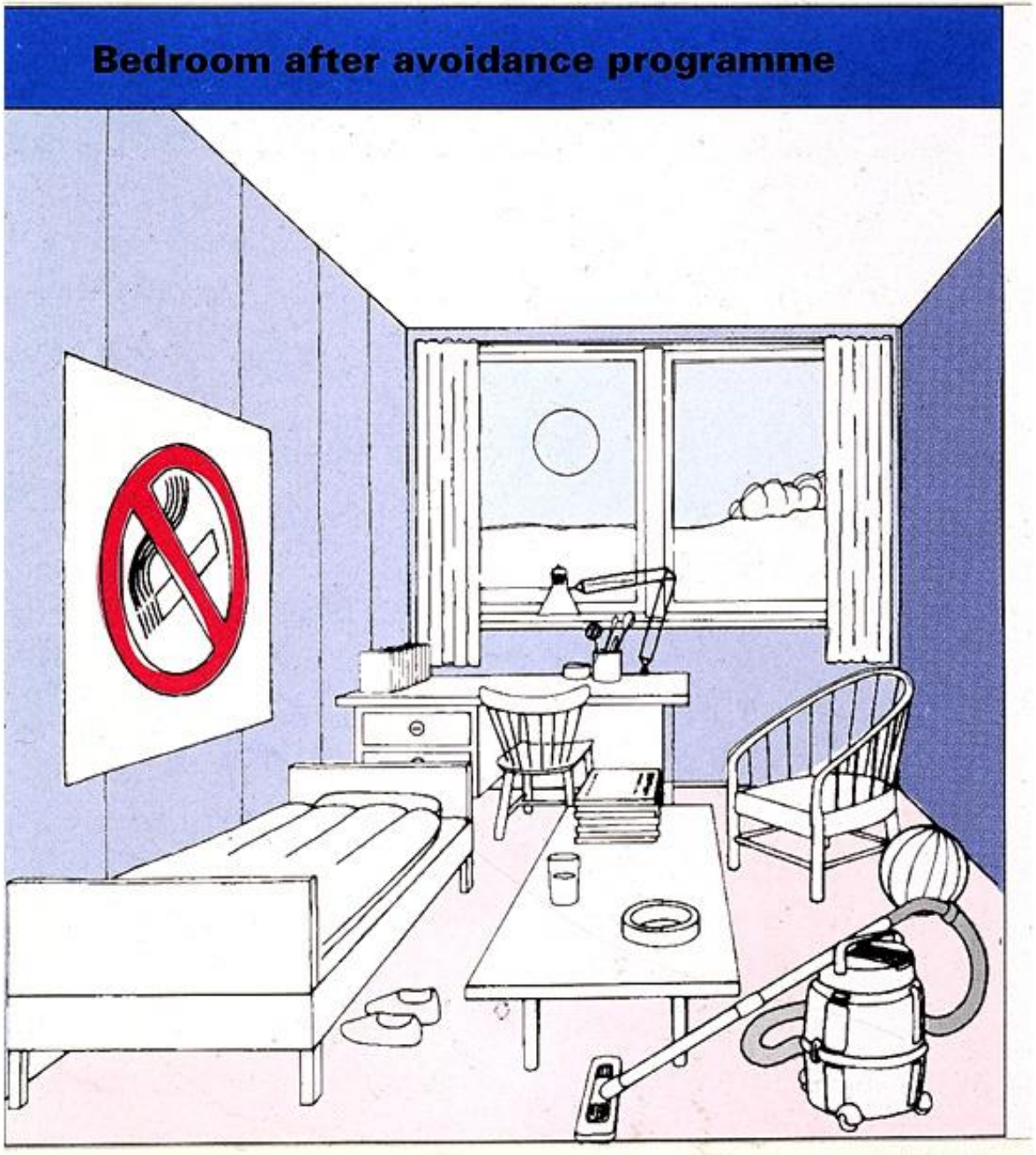
Global Initiative for Asthma. 2023 GINA Report, Global Strategy for Asthma Management and Prevention.

氣喘的其他預防

- 提高 omega-3 攝取可以減少室內PM2.5 引發氣喘的症狀
  - ✓二手菸, 三手菸, 電子菸
  - ✓灰塵
  - ✓廚房油煙
  - ✓燒香
  - ✓鄰近主要幹道空汙

Am J Respir Crit Care Med. 2019 Jun 15;199(12):1478-1486


Bedroom before avoidance programme


Bedroom after avoidance programme


H
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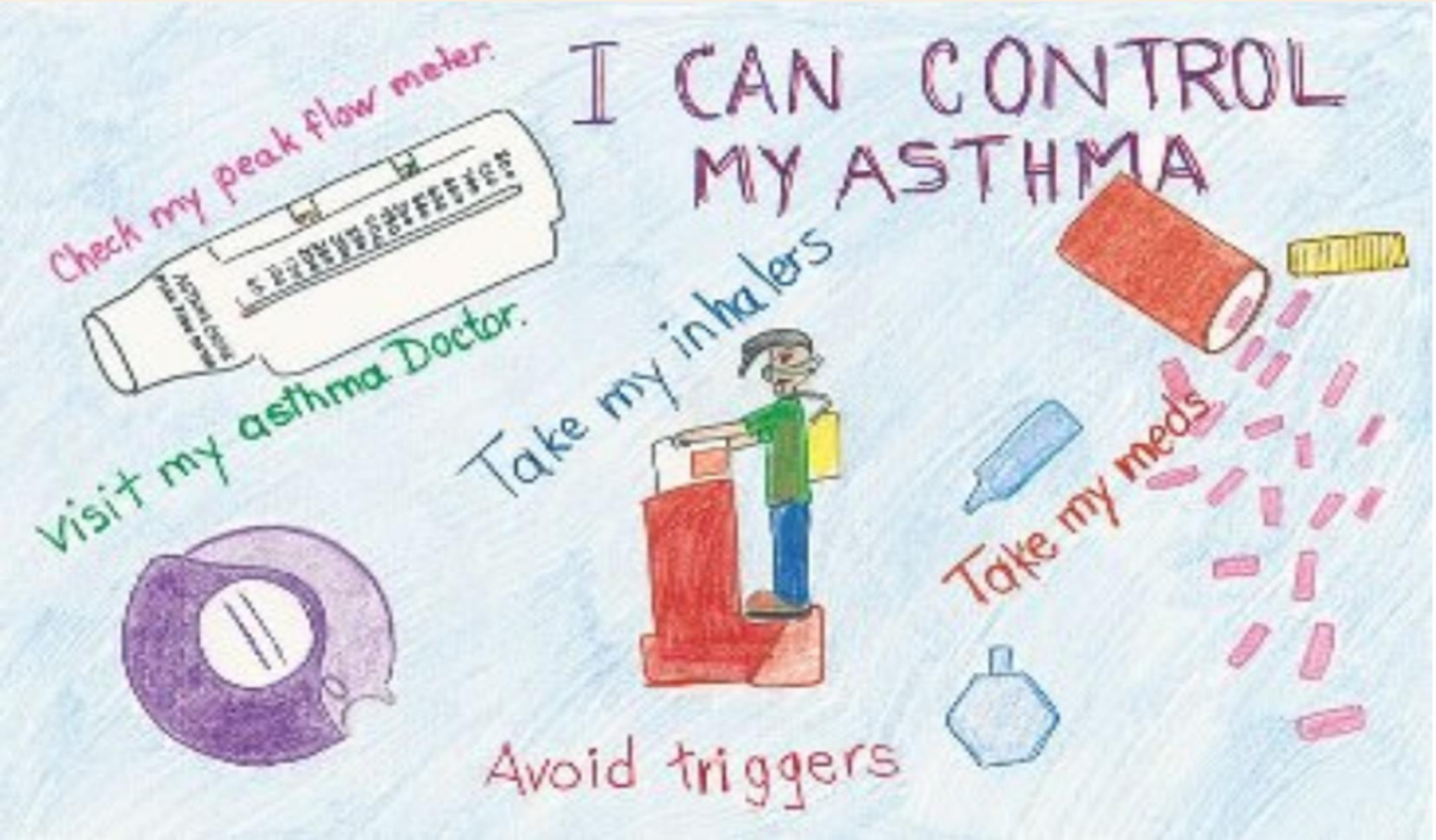
wikiHow to Remove Bathroom Mold

結　論


I CAN CONTROL MY ASTHMA
Check my peak flow meter.
Visit my asthma Doctor.
Take my inhalers
Take my meds
Avoid triggers

TAKE home message (I)

- 兒童的氣喘臨床症狀多變且非特異性，病理特徵往往無法常規地被評估
- **發病年齡、性別、每次氣喘發作的嚴重度與頻率、異位性體質與相關疾病、家族史或肺功能不正常**都是好犯兒童氣喘的危險因子
- 6-11 歲學齡兒童能夠適用與成人相同的評估與檢測方式，惟標準不同
- 5 歲以下兒童因不適用成人檢測方式，應留心臨床症狀的表現與利用其他方式進行診斷
- 孩童為有良好預後，氣喘確診後盡早開始控制型藥物之治療(**幾乎所有病人都可建議**)

TAKE home message (II)

- 5 歲以下兒童出現以下症狀需**高度懷疑**有氣喘存在
  - 頻繁喘鳴發作多於 1 個月 1 次
  - 運動後即誘發咳嗽或喘鳴
  - 無病毒感染時夜咳
  - 喘鳴無季節性差異
  - 症狀持續到大於 3 歲
- 欣流®目前的證據認為是安全的，但是要請醫師及家長多加留意
- **兒童若出現急性氣喘發作時的評估很重要, 才不會耽誤病人之安全**
- **個人化的氣喘治療**為未來發展的趨勢，根據個人的生化指標等選擇最適當的生物製劑使用，可以大幅改善治療的效果


謝謝聆聽 !!
Any comment ?