

嬰幼兒氣喘病

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Asthma : definition ?

- Wheeze +
- allergy +
- bronchial
hyperresponsiveness
- = asthma

氣喘的定義

- 氣喘是一種反覆發作的氣流阻礙病變，會自行緩解或是經過適當的治療而恢復。依其嚴重的程度可以呈現呼吸困難、喘鳴音、胸悶和咳嗽等症狀，有些氣喘患者會出現多痰。氣喘是一種會出現不同症狀及導致氣流阻滯的慢性氣道疾病。氣喘發作可能非常迅速也可能是緩慢出現。通常症狀不是很嚴重，但是急性惡化時可能非常嚴重，若未給予有效的治療也可能會致命。

氣喘的定義

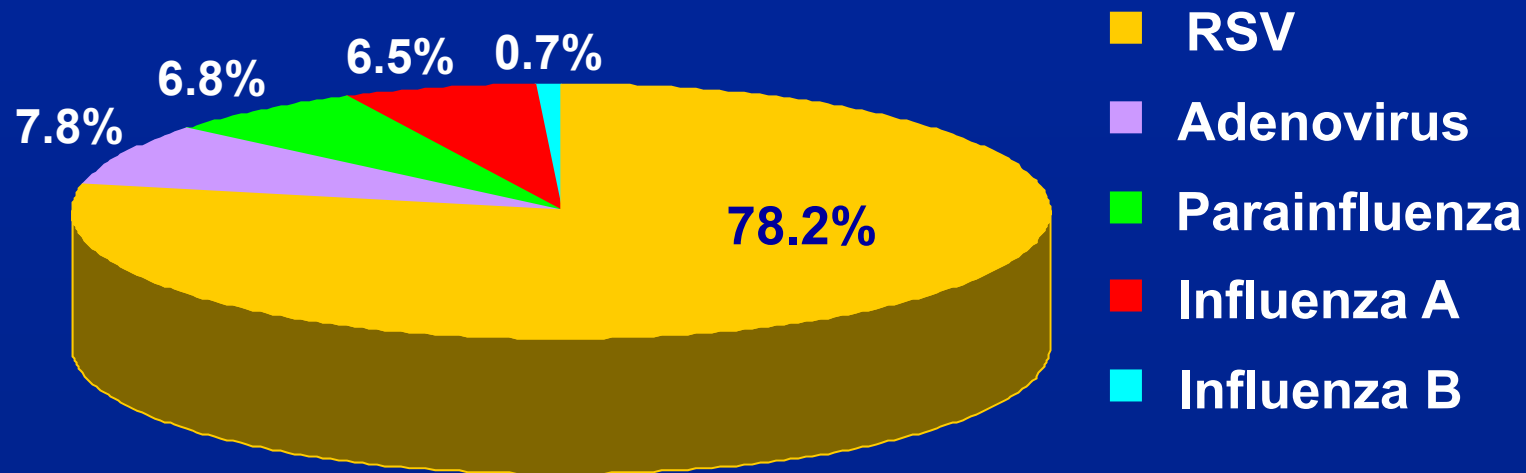
- 氣喘是一種氣道的慢性發炎，其中有許多細胞參與，包括肥大細胞、嗜伊紅性白血球及T淋巴球。在容易發病的人，此種發炎會導致反覆喘鳴、呼吸困難、胸悶、以及夜間及清晨的咳嗽。這些症狀通常合併氣流阻滯，此種變化可因治療而回復（部份或完全）。此種發炎也會增加氣道對不同刺激的反應度。

What Is Bronchiolitis?

- Bronchiolitis is acute inflammation of the airways, characterised by wheeze
- Bronchiolitis can result from a viral infection
- Respiratory Syncytial Virus (RSV) may be responsible for up to 90% of bronchiolitis cases in young children

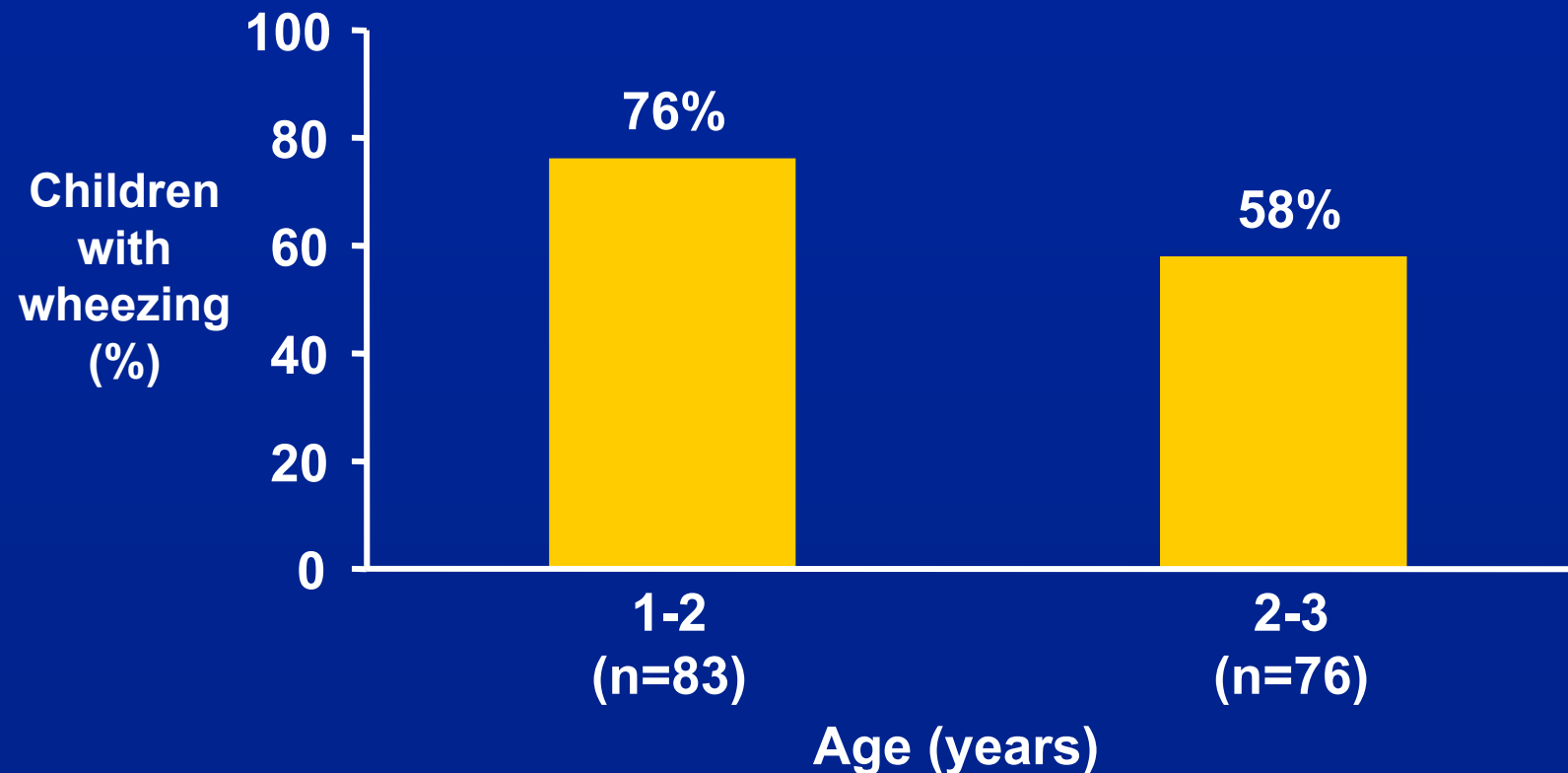
RSV Is a Common Virus Causing Bronchiolitis in Children

- In a clinical study in Argentina, RSV was the most common virus isolated from a sample of children aged <5 years with acute lower respiratory infection



Wheezing Often Persists After Bronchiolitis

- In a study of 83 children aged <2 years hospitalised with bronchiolitis, a large proportion had subsequent wheezing

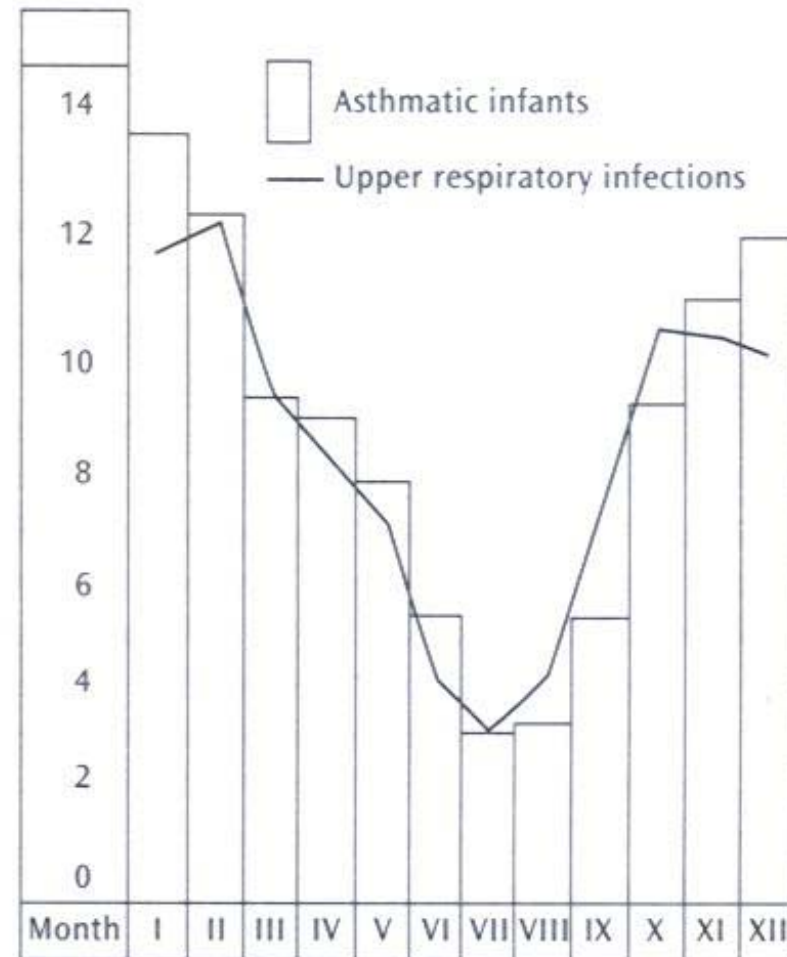


Korppi M et al. *Am J Dis Child* 1993;146:628-631

Terminology

- Wheezy bronchitis
- Wheezy baby syndrome
- Wheezing LRI
- Wheeze-associated respiratory illness
- Recurrent bronchiolitis
- Infantile asthma
- Asthma

Pediatric asthma and wheeze usually comes with viral respiratory infection.



80% of all the children who had asthmatic symptoms during the first year of life became symptom free before the age of 6–11

Figure 9.1 *Concordance of community reporting of upper respiratory infections and admissions to one hospital with acute severe asthma in the first year of life. (From ref. 1 with permission.)*

Epidemiology of wheeze

- No less than 30% of all children have at least one attack of bronchial obstruction during the first 3 years of life. (Eur Respir J 2000;15:151-7)
- Peak incidence rates occur between the age of 3 and 6 months. (Pediatrics 1991;87:190-8)
- The frequency of new cases decreases markedly after the end of the first year.
- In developed countries, no less than 60% of all infants and young children who have one or more episodes of wheezing during the first 3 years of life will have stopped wheezing by the early school years. (N Engl J Med 1995;332:133-8)

Wheeze is a symptom, not a diagnosis.

- 1960s. Infant wheezing disorders differed in important ways from childhood asthma. Episodic; associated with URI; grow out of it.
- 1970s and 1980s. Favor “asthma”. Epidemic of childhood asthma and awareness that under-diagnosis and under treatment lead to morbidity and mortality; availability of therapeutic agents.

Factors which indicate increased suspect of asthma in childhood asthma with wheeze

Risk factor	Size of effect
Parental asthma	+++
Personal eczema	+++
Wheeze without colds	++
Several episodes of wheeze	++
Older age at onset of wheeze	++
Allergic rhinitis	+
Eosinophilia (>95% CI)	+
Raised EPX or ECP	+
Serum soluble IL-2R	+
Cockroach allergen load	+
Prematurity	+

Natural history

- Childhood asthma as a heterogeneous disease.
 - Persistent wheezing after RSV infection.
 - Atopy-associated asthma.
 - Transient wheezing of infancy.

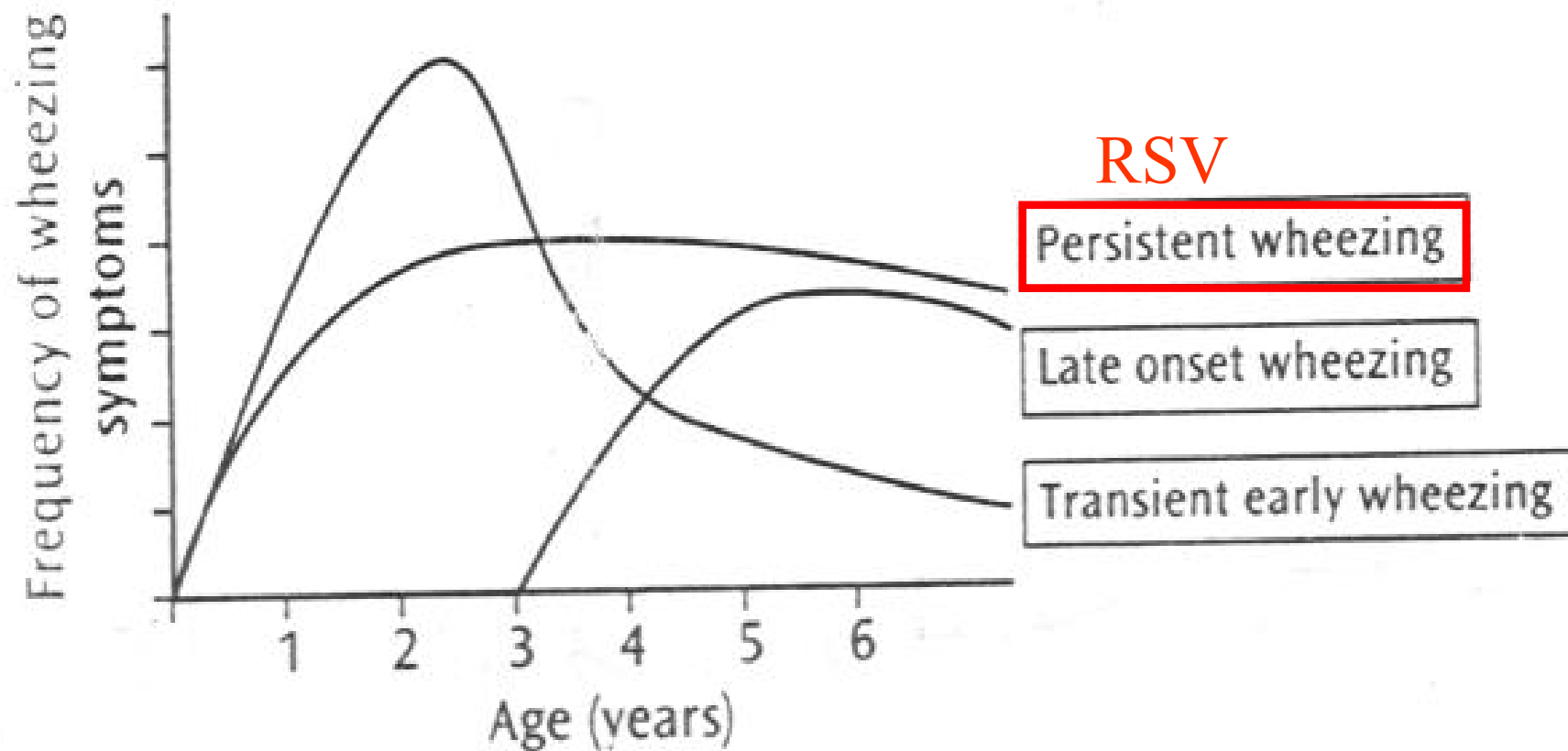
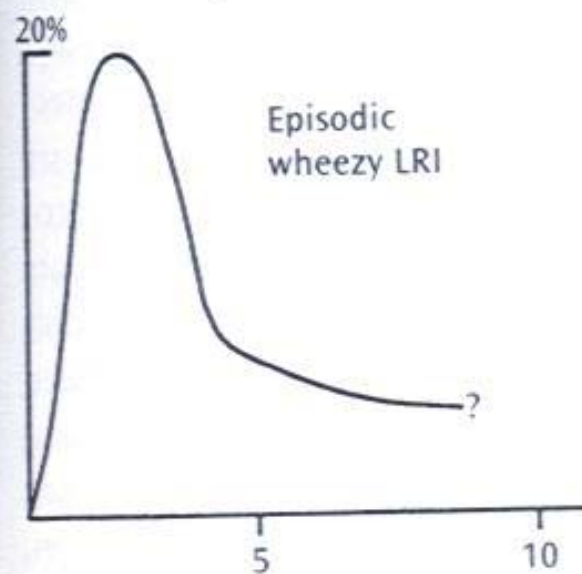
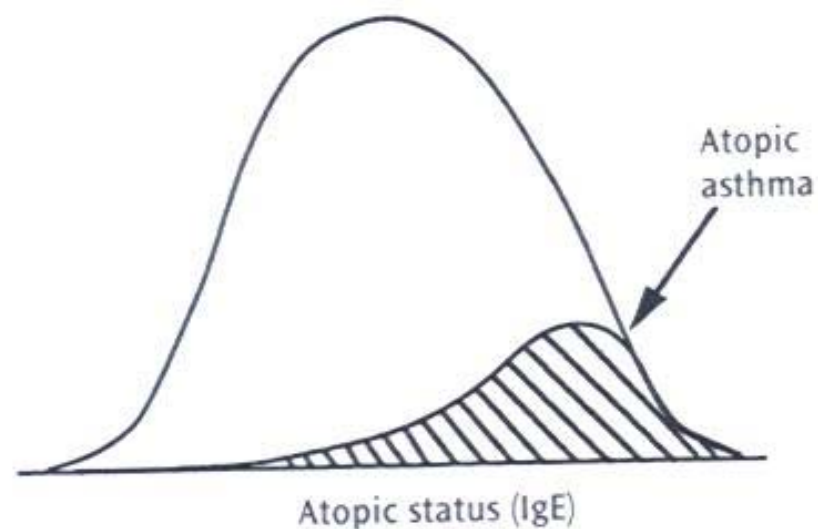
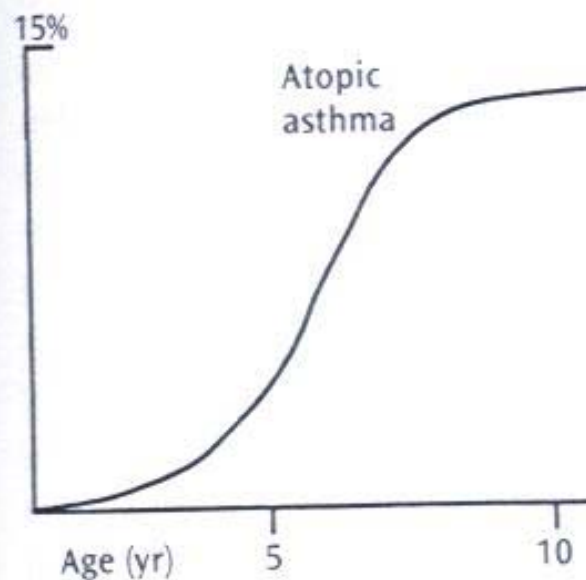
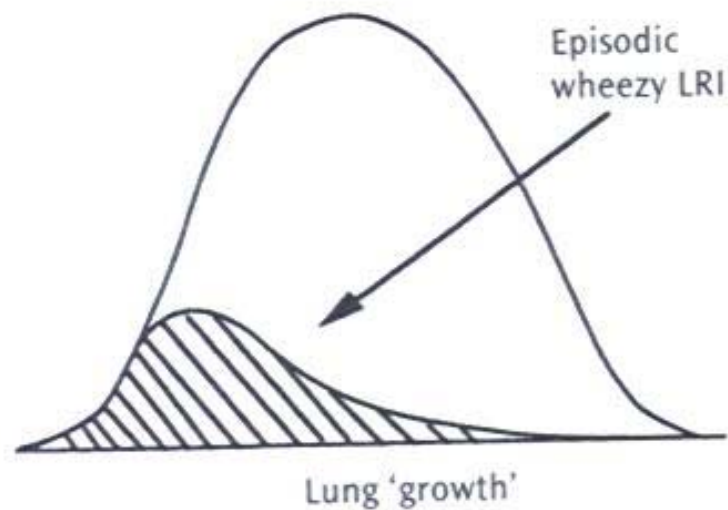


Figure 2.1 Schematic depiction of putative development of wheezing during childhood. Difference in prognosis and natural history of symptoms in three distinct groups of wheezing children. [N Engl J Med 1995;332:133-8](#)

Population point prevalence

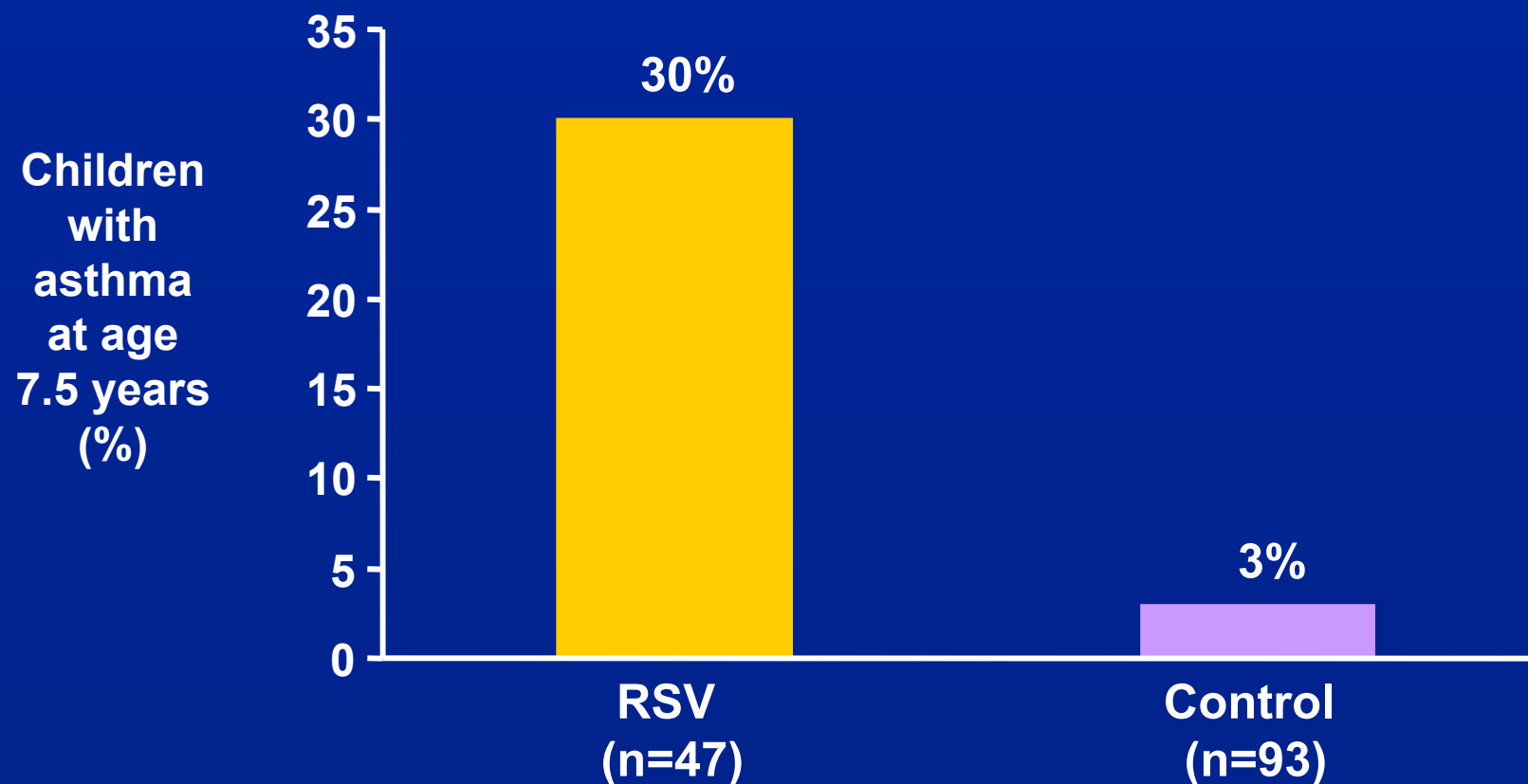


Distribution of affected individuals in the whole population



RSV-Induced Bronchiolitis May Be Associated With the Development of Asthma

- In a study of 140 children, the incidence of asthma at age 7.5 years was higher in children who had been infected with RSV in infancy compared with matched controls



Sigurs N et al. *Am J Respir Crit Care Med* 2000;161:1501-1507

有喘鳴症狀幼兒的鑑別診斷

年齡	常見原因	較不常見的原因	罕見原因
六個月以下	細支氣管炎 胃食道逆流	吸入性肺炎* 支氣管肺發育不良 鬱血性心衰竭	氣喘 呼吸道異物 呼吸道或週邊組織先天異常 囊狀纖維化†
六個月 ~ 二歲	細支氣管炎 呼吸道異物	吸入性肺炎* 氣喘 支氣管肺發育不良 胃食道逆流	鬱血性心衰竭 呼吸道或週邊組織先天異常 囊狀纖維化†
二 ~ 五歲	氣喘	病毒性肺炎 呼吸道異物	吸入性肺炎* 細支氣管炎 鬱血性心衰竭
年紀越小的喘鳴 越需考慮其他的疾病原因			呼吸道或組織先天異常

Treatment

- -
 -
 -
 -
 -

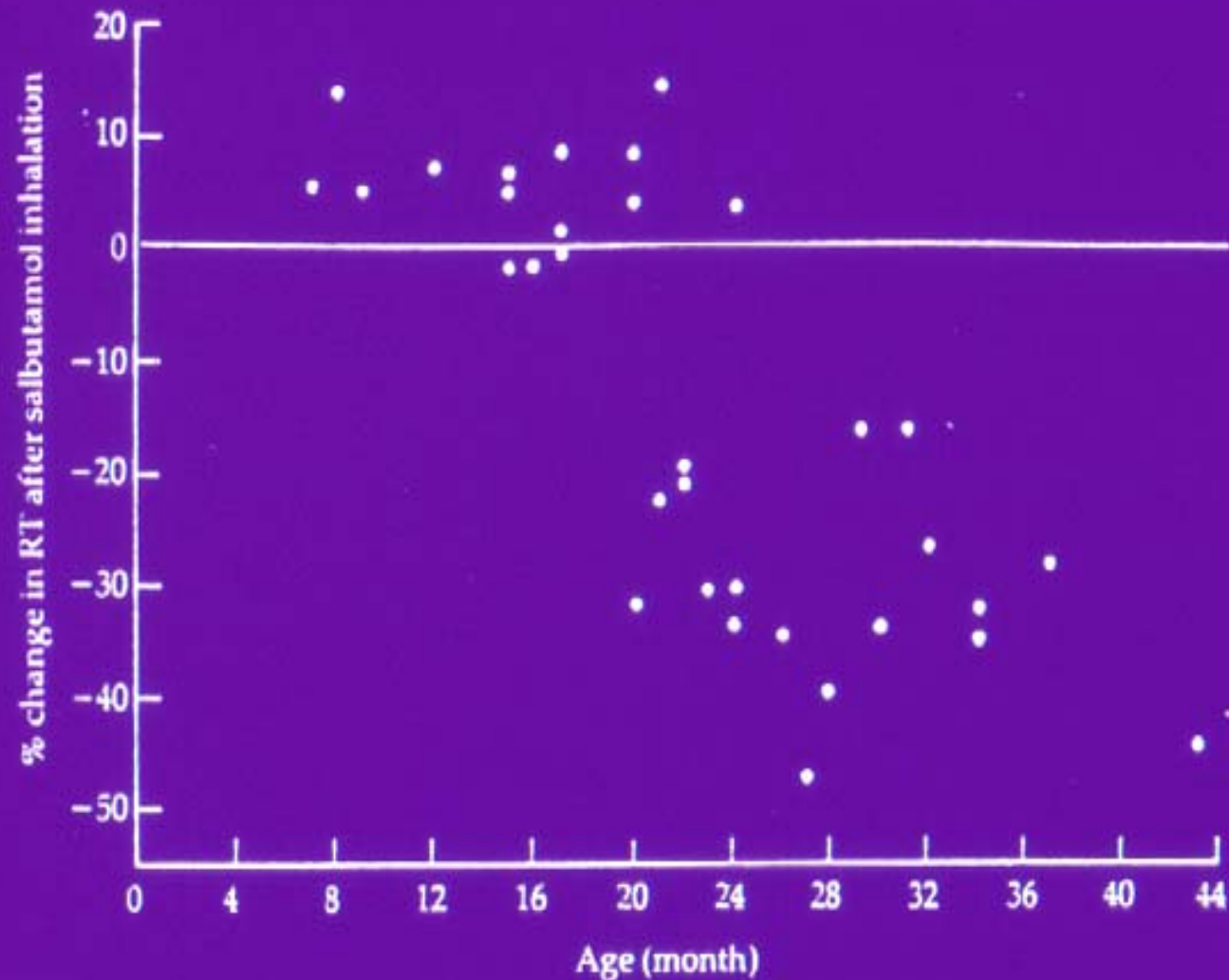


Figure 5.12 Effects of inhaled β_2 stimulants (salbutamol 2.5 mg) on total respiratory resistance. No child under twenty months showed a significant improvement (ie a fall in RT).

At what age do bronchodilator work? Arch Dis Child 1978;53:532-5.

Lin YZ et al.. Clinical trial of corticosteroid and beta-2 bronchodilator in young wheezy patients. Acta Paed Sin 1991;32:333-40.

- Two-thirds of the quick responders to hydrocortisone and procaterol were 12 months old or older. The personal and family allergic history, serum IgE level, and total eosinophil count could not be used as parameter to predict responsiveness to the combined therapy of hydrocortisone and procaterol.

Hsiao YC, Lin YZ, Chen W, Wu Kw. Respiratory failure after nebulized terbutaline treatment in severely wheezy infants: Report of three cases. Acta Paed Sin 1994;35:244-9.

- Admitted due to respiratory distress.
- Prematurity
- Case 1: 11m/o, Wilson-Mikity syndrome;
- Case 2: 5m/o, BPD;
- Case 3: 13m/o, BPD

Causes of oxygen desaturation after inhalation treatment

- **Ventilation-perfusion ratio**
- **Change of pH, acidity**
- **Osmolality**
- **Drop of temperature**

Bronchodilators (I)

- While clinicians recognized a clinical response in some patients, former clinical trials had shown little benefit.
- A single dose of nebulized albuterol in infants with acute wheeze or bronchiolitis or after recovery commonly leads to a transient worsening of hypoxemia and no change or even a diminution in forced expiratory flows by the squeeze technique.
- Airway resistance changes little or seems to improved.

Bronchodilators (II)

- There is no evidence for an overall beneficial clinical effect of nebulized β 2-agonists in acute severe episodes in infancy or acute bronchiolitis, although some infants may seem to respond. A systemic review suggested marginal benefits in recurrent episodes in children in the first 2 year of life.
- Regular short-acting inhaled β 2-agonist therapy is no better than placebo in infants with chronic wheeze.

醫生，這一招到底
有沒有用？



The efficacy of corticosteroid therapy in wheezy infants and preschool children

			Chronic wheeze	
therapy	Acute viral bronchiolitis	Episodic viral wheeze	episodic	Interval symptoms
acute therapy				
Inhaled	0	<u>+</u>	?	-
Oral	0	?	?	-
Chronic therapy	0*	0	+	++

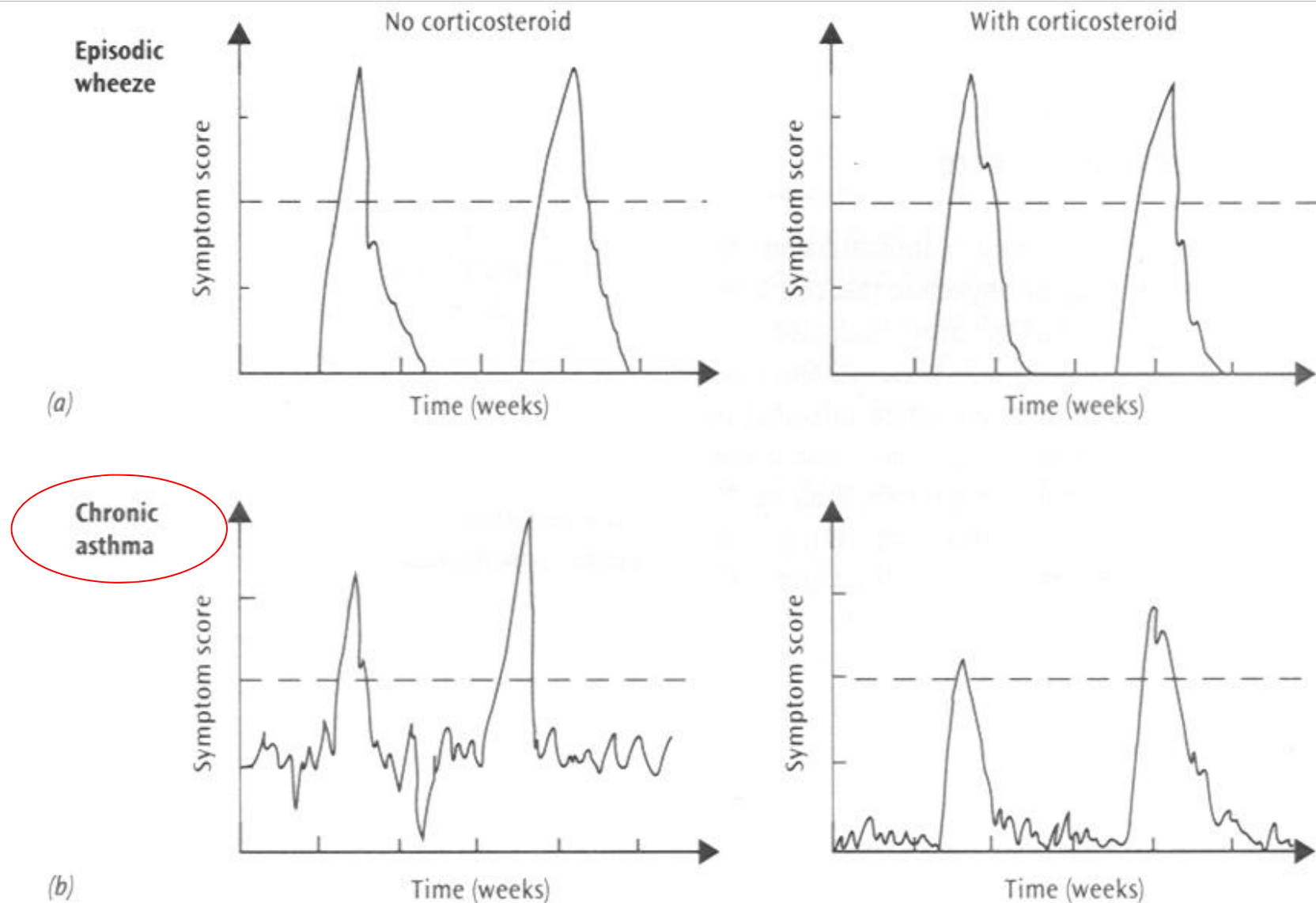


Figure 9.7 Possible explanation for the apparent paradox that inhaled corticosteroid preventer therapy (a) appears to have little or no effect on acute attacks of purely episodic viral wheeze (without interval symptoms), but (b) ameliorates episodes in children with chronic asthma (with interval symptoms as well as acute episodes), by reducing the variable baseline of interval symptoms.

Scope of the Problem

Administration

- Inhaled therapies can be difficult to administer



嬰幼兒哮鳴與氣管擴張劑之使用

林應然 黃富源¹

Act Paediatr Tw 2005;46:3-5.

- 嬰幼兒哮鳴與氣管擴張劑之使用是臨床兒科的一個重要領域，臨床上雖然很難鑑定嬰幼兒哮鳴是否會發展成日後的氣喘病，或只是單純會自然痊癒的病毒性細支氣管炎，但大多數的嬰幼兒哮鳴只是暫時性的，與出生時之肺功能較差有關，不見得與過敏氣喘發生牽連。整體而言，吸入性氣管擴張劑對嬰幼兒哮鳴沒有多大效用，雖然在某些個案中或許有些效果。

氣喘的嚴重度分級及治療原則

第四階：重度持續性氣喘

治療前臨床症狀

持續有症狀
經常發作
經常有夜間症狀
運動受限

- $FEV_1 \leq 60\%$ 預估值；
或 $PEF \leq 60\%$ 最佳值
- PEF 每日變異度 $> 30\%$

每日所需氣喘控制藥物

多種控制藥物：包括吸入式乙二型交感神經興奮劑，必要時在加：緩釋型茶鹼製劑，白三烯受體拮抗劑、長效口服乙二型交感神經興奮劑

第三階：中度持續性氣喘

治療前臨床症狀

每日有症狀
發作時影響活動及睡眠
夜間症狀每週一次以上
每日需使用短效乙二型交感神經興奮劑

- $FEV_1 60-80\%$ 預估值；
或 $PEF 60-80\%$ 最佳值
- PEF 每日變異度 $> 30\%$

每日所需氣喘控制藥物

包括吸入低劑量或中劑量類固醇，加上長效吸入式乙二型交感神經興奮劑（特別為控制夜間症狀）

第二階：輕度持續性氣喘

治療前臨床症狀

白天症狀頻率每週一次或一次以上但少於每日一次
發作時可能影響活動及睡眠
夜間症狀頻率每月兩次以上

- $FEV_1 \geq 80\%$ 預估值；
或 $PEF \geq 80\%$ 最佳值
- PEF 每日變異度 20- 30%

每日所需氣喘控制藥物

吸入低劑量類固醇，必要時可加入一種長效支氣管擴張劑（特別為控制夜間症狀）

第一階：輕度間歇性氣喘

治療前臨床症狀

白天症狀頻率每週少於一次（輕度發作）
夜間症狀頻率每月不超過兩次，不發作時無症狀而且肺功能正常

- $FEV_1 \geq 80\%$ 預估值；或 $PEF \geq 80\%$ 最佳值
- PEF 每日變異度 $< 20\%$

氣喘控制藥物

- 必要時使用吸入式速效乙二型交感神經興奮劑*
- 所需治療之藥物取決於發作之嚴重度

*見第17頁

請大家思考：

嬰幼兒過敏氣喘如何診斷？

嬰幼兒過敏氣喘如何分級？

嬰幼兒過敏氣喘如何治療？

嬰幼兒過敏氣喘如何預防？

STEP 1: Intermittent

Symptoms less than once a week

Brief exacerbations

Nocturnal symptoms not more than twice a month

- FEV_1 or PEF $\geq 80\%$ predicted
- PEF or FEV_1 variability $< 20\%$

STEP 2: Mild Persistent

Symptoms more than once a week but less than once a day

Exacerbations may affect activity and sleep

Nocturnal symptoms more than twice a month

- FEV_1 or PEF $\geq 80\%$ predicted
- PEF or FEV_1 variability 20 to 30%

- **STEP 3: Moderate Persistent**

Symptoms daily

Exacerbations may affect activity and sleep

Nocturnal symptoms more than once a week

Daily use of inhaled short-acting beta2-agonist

- FEV₁ or PEF 60 to 80% predicted
- PEF or FEV₁ variability >30%
-

- **STEP 4: Severe Persistent**

Symptoms daily

Frequent exacerbations

Frequent nocturnal asthma symptoms

Limitation of physical activities

- FEV₁ or PEF \leq 60% predicted
- PEF or FEV₁ variability >30%

氣喘的長期治療：階梯式的治療方式（五歲以下兒童）

粗體字為建議的治療方式

注意：
治療必須根據患者的嚴重度決定由那一階開始。但在任何一階都可視情況需要先給予一短期（5-7天）的口服類固醇。

第四階：重度持續性氣喘

控制藥物*

每日必須使用

- 吸入高劑量類固醇加下列藥物1種
- 口服糖
- 1. 糖類型茶碱
- 2. 長效吸入式乙二型交感神經興奮劑
- 3. 白三烯受體拮抗劑*
- 4. 口服類固醇

緩解藥物*

- 速效支氣管擴張劑：有症狀時使用速效吸入式乙二型交感神經興奮劑

第三階：中度持續性氣喘

控制藥物*

每日必須使用

- 吸入中劑量類固醇，替代方案有四：
- 1. 吸入中劑量類固醇加糖類型茶碱
- 2. 吸入中劑量類固醇加長效吸入式乙二型交感神經興奮劑
- 3. 吸入高劑量類固醇
- 4. 吸入中劑量類固醇加白三烯受體拮抗劑*

緩解藥物*

- 速效支氣管擴張劑：有症狀時使用速效吸入式乙二型交感神經興奮劑，但是每天不超過4次。

第二階：輕度持續性氣喘

控制藥物*

每日必須使用

- 吸入低劑量類固醇，替代方案有三：
- 1. 糖類型茶碱
- 2. 口服茶碱(Intal)
- 3. 白三烯受體拮抗劑*

緩解藥物*

- 速效支氣管擴張劑：有症狀時使用速效吸入式乙二型交感神經興奮劑，但是每天不超過4次。

第一階：間歇發作性氣喘

控制藥物*

- 不須使用

緩解藥物*

- 有症狀時使用短效吸入式乙二型交感神經興奮劑，但是每週不超過1次
- 所需治療之藥物劑量取決於發作之嚴重度
- 運動前吸鼻露過敏原時，使用短效或長效吸入式乙二型交感神經興奮劑或Intal

降階治療

每三到六個月評估一次治療計畫。
● 若氣喘病情已達良好控制狀況且持續三個月以上，可循序降階治療。

升階治療

若病情無法達到良好控制時需考慮升階治療。但首先需檢查患者使用藥物的方法、對治療的遵從性、以及環境控制是否良好（必須避開過敏原及各種誘發因素）。

在每一階均須注意預防或控制誘發因素

* 速效藥包括短效藥及長效藥之Formoterol(見第10頁)。

此處吸入式類固醇之劑量請參照第10頁所列。

★ 有年齡的限制，其年齡下限是：Montelukast和Pranlukast是2歲，Zafirlukast是7歲。

請大家思考：

嬰幼兒過敏氣喘如何診斷？

嬰幼兒過敏氣喘如何分級？

嬰幼兒過敏氣喘如何治療？

嬰幼兒過敏氣喘如何預防？

Figure 7-8. Recommended Medications by Level of Severity for Children Younger Than 5 Years of Age

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β_2 -agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

Level of Severity**	Daily Controller Medications	Other Treatment Options***
Step 1 Intermittent Asthma****	<ul style="list-style-type: none"> • None necessary 	
Step 2 Mild Persistent Asthma	<ul style="list-style-type: none"> • Low-dose inhaled glucocorticosteroid 	<ul style="list-style-type: none"> • Sustained-release theophylline, <i>or</i> • Cromone, <i>or</i> • Leukotriene modifier
Step 3 Moderate Persistent Asthma	<ul style="list-style-type: none"> • Medium-dose inhaled glucocorticosteroid 	<ul style="list-style-type: none"> • Medium-dose Inhaled glucocorticosteroid <i>plus</i> sustained-release theophylline, <i>or</i> • Medium-dose Inhaled glucocorticosteroid <i>plus</i> long-acting oral β_2-agonist, <i>or</i> • High-dose inhaled glucocorticosteroid <i>or</i> • Medium-dose Inhaled glucocorticosteroid <i>plus</i> leukotriene modifier
Step 4 Severe Persistent Asthma	<ul style="list-style-type: none"> • High-dose Inhaled glucocorticosteroid <i>plus</i> long-acting inhaled β_2-agonist, <i>plus</i> one or more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid 	

All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

* Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β_2 -agonist, and short-acting theophylline.

** See *Figure 5-6* and *Figure 5-7* for classification of severity.

*** Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.

**** Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (*Evidence D*).

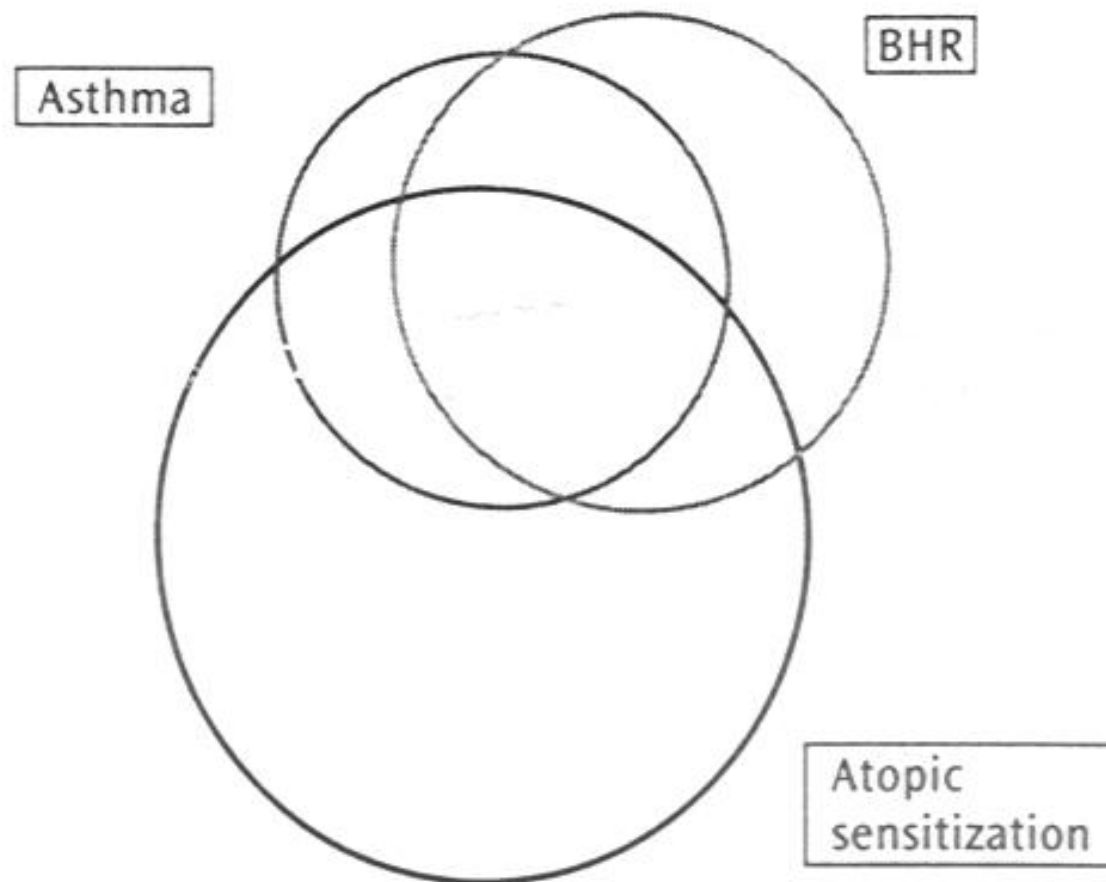


Figure 2.2 *Schematic depiction of the relationship between asthma, bronchial hyperresponsiveness (BHR) and atopic sensitization in school-children. While most school-aged children with asthma also display signs of BHR and atopic sensitization the majority of children labelled atopic do not suffer from respiratory symptoms.*

Table 1. Risk factors in transient wheezing of infancy and atopic asthma

Transient wheezing of infancy	Atopic asthma
Diminished airway function at birth	Family history of allergy
Exposure to viral infection	Personal history of allergy
Tabacco smoke exposure in utero	Wheeze without colds
Tabacco smoke exposure after birth	Repeated episodes of wheeze
Low socioeconomic status	Older age at onset of wheeze
Prematurity	Aeroallergen exposure
Not breast fed	Exposure to viral infection
Male sex	Tabacco smoke exposure after birth
	Prematurity
	Eosinophilia
	Low socioeconomic status
	Male sex

- Inhaled glucocorticosteroids are at present the most effective controller medications and are therefore recommended for persistent asthma at any step of severity. Long-term treatment with inhaled glucocorticosteroids markedly reduces the frequency and severity of exacerbations.
- Long-term treatment with inhaled glucocorticosteroids has not been shown to be associated with any increase in osteoporosis or bone fracture. Studies including a total of over 3,500 children treated for mean periods of 1 to 13 years have found no sustained adverse effect of inhaled glucocorticosteroids on growth.
- Rapid-acting inhaled β_2 -agonists are the most effective reliever therapy in asthma, and this class of drugs has been the mainstay of asthma treatment in children for many years. These drugs are the most effective bronchodilators available and are therefore the treatment of choice for acute asthma symptoms.
- Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

**Figure 7-5. Recommended Medications by Level of Severity:
Adults and Children Older Than 5 Years of Age**

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β_2 -agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

Level of Severity**	Daily Controller Medications	Other Treatment Options***
Step 1 Intermittent Asthma****	<ul style="list-style-type: none"> • None necessary 	
Step 2 Mild Persistent Asthma	<ul style="list-style-type: none"> • Low-dose inhaled glucocorticosteroid 	<ul style="list-style-type: none"> • Sustained-release theophylline, <i>or</i> • Cromone, <i>or</i> • Leukotriene modifier
Step 3 Moderate Persistent Asthma	<ul style="list-style-type: none"> • Low-to-medium inhaled glucocorticosteroid <i>plus</i> long-acting inhaled β_2-agonist 	<ul style="list-style-type: none"> • Medium-dose Inhaled glucocorticosteroid <i>plus</i> sustained-release theophylline, <i>or</i> • Medium-dose Inhaled glucocorticosteroid <i>plus</i> long-acting oral β_2-agonist, <i>or</i> • High-dose inhaled glucocorticosteroid <i>or</i> • Medium-dose Inhaled glucocorticosteroid <i>plus</i> leukotriene modifier
Step 4 Severe Persistent Asthma	<ul style="list-style-type: none"> • High-dose Inhaled glucocorticosteroid <i>plus</i> long-acting inhaled β_2-agonist, <i>plus</i> one or more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid • Anti-IgE***** 	

All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

* Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β_2 -agonist, and short-acting theophylline.

** See Figure 5-6 and Figure 5-7 for classification of severity.

*** Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.

**** Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (Evidence D).

***** Current evidence supports use in adults and children 12 years and above only.

KEY POINTS:

- Childhood and adult asthma share the same underlying pathophysiological mechanisms. However, because of the processes of physical and cognitive growth and development, the effects, and adverse effects, of asthma and asthma treatments in children differ from those in adults.
- Many asthma medications (e.g., glucocorticosteroids, β_2 -agonists, theophylline) are metabolized faster in children than in adults, and young children tend to metabolize drugs faster than older children.
- Therapy should be selected on the basis of the severity of asthma in the individual patient, the availability of antiasthma medications, the characteristics of the health care system, and the individual patient's social, family, and economic circumstances.

Burden of Disease

- **RSV is the most common reason for hospitalisation of infants with acute respiratory illness**
 - From 1994-1996 an estimated 50,000-80,000 children were hospitalised in the USA
- **In the USA, RSV accounts for up to 50% of all hospitalisation admissions for bronchiolitis**
- **The hospitalisation rate for bronchiolitis is increasing**
 - There was a 2.4-fold increase from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996 in the USA

Shay DK et al. *JAMA* 1999;282:1440-1446; La Via WV et al. *J Pediatr* 1992;121:503-510;
Kimpen JL. *Respir Res* 2002;3(Suppl 1):S40-S45

Differential diagnosis of wheeze

Table 6a.3 *Conditions other than asthma and bronchiolitis which can cause wheezing*

Infection

Wheeze rare in infants with non-viral infections

M. pneumoniae infection causes acute wheezing in 30%

Tuberculosis: focal wheezing; CXR changes

Genetic Disorder

Cystic fibrosis: rarely uncomplicated wheezing

Immune deficiencies: cause bacterial infections, but rarely wheeze

Primary ciliary dyskinesia:

- symptoms from early infancy
- wheeze not prominent

Congenital Abnormalities

Tracheo-oesophageal fistula: CXR changes

Other airway abnormalities:

- early onset; unusual noises such as biphasic stridor
- radiology helpful

Miscellaneous

Gastro-oesophageal reflux: wheeze with or without aspiration

Foreign body aspiration

- suggestive history in 80%; focal signs; radiology
-

Clinically important reasons for differentiating between types of asthma (phenotypes)

- Responses to treatment
- Causes (therefore preventive programs)
- Natural history (prognosis)
- Genetic basis

RSV induced wheeze

Who is to be blamed first ?

- RSV causes lung damage, leading to recurrent wheeze.
- RSV picks out infants at a particularly early age who are susceptible to recurrent wheezy LRI.
- Both

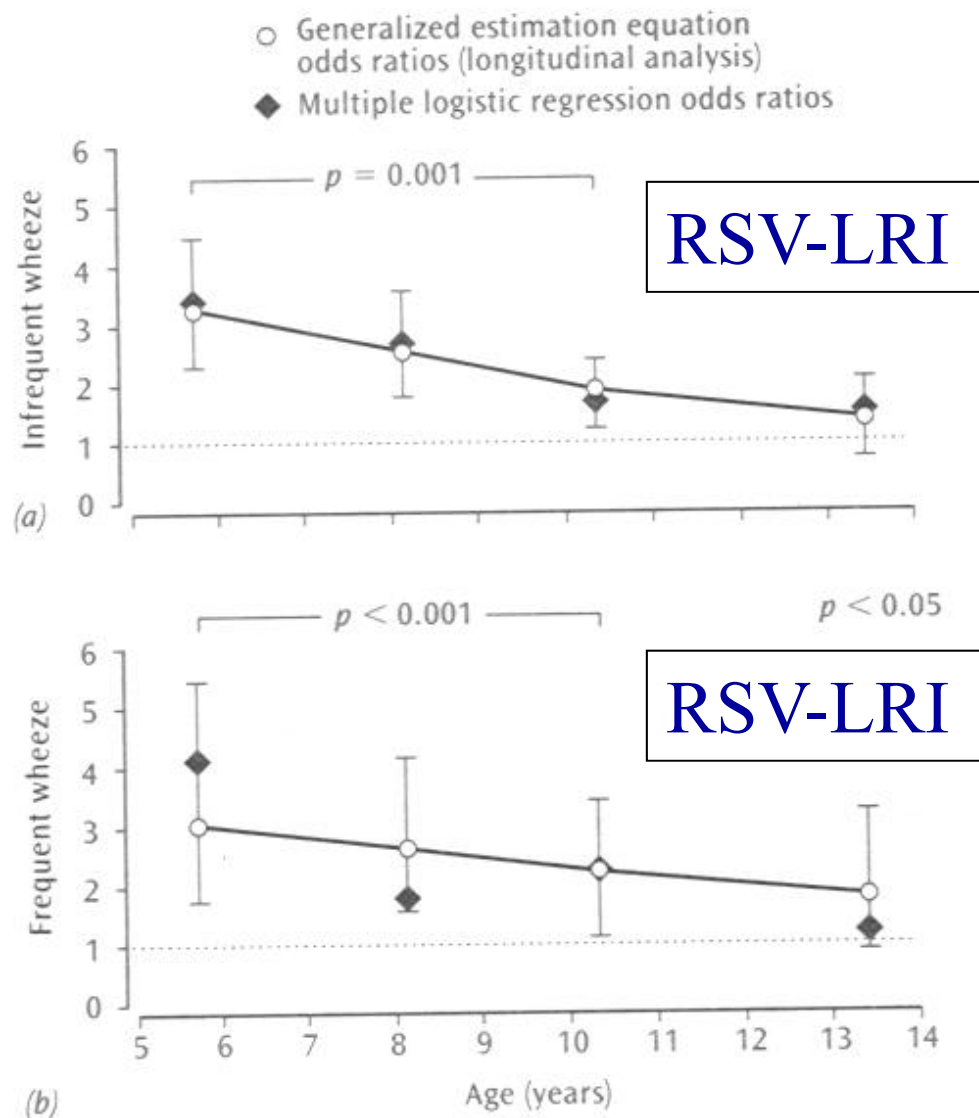
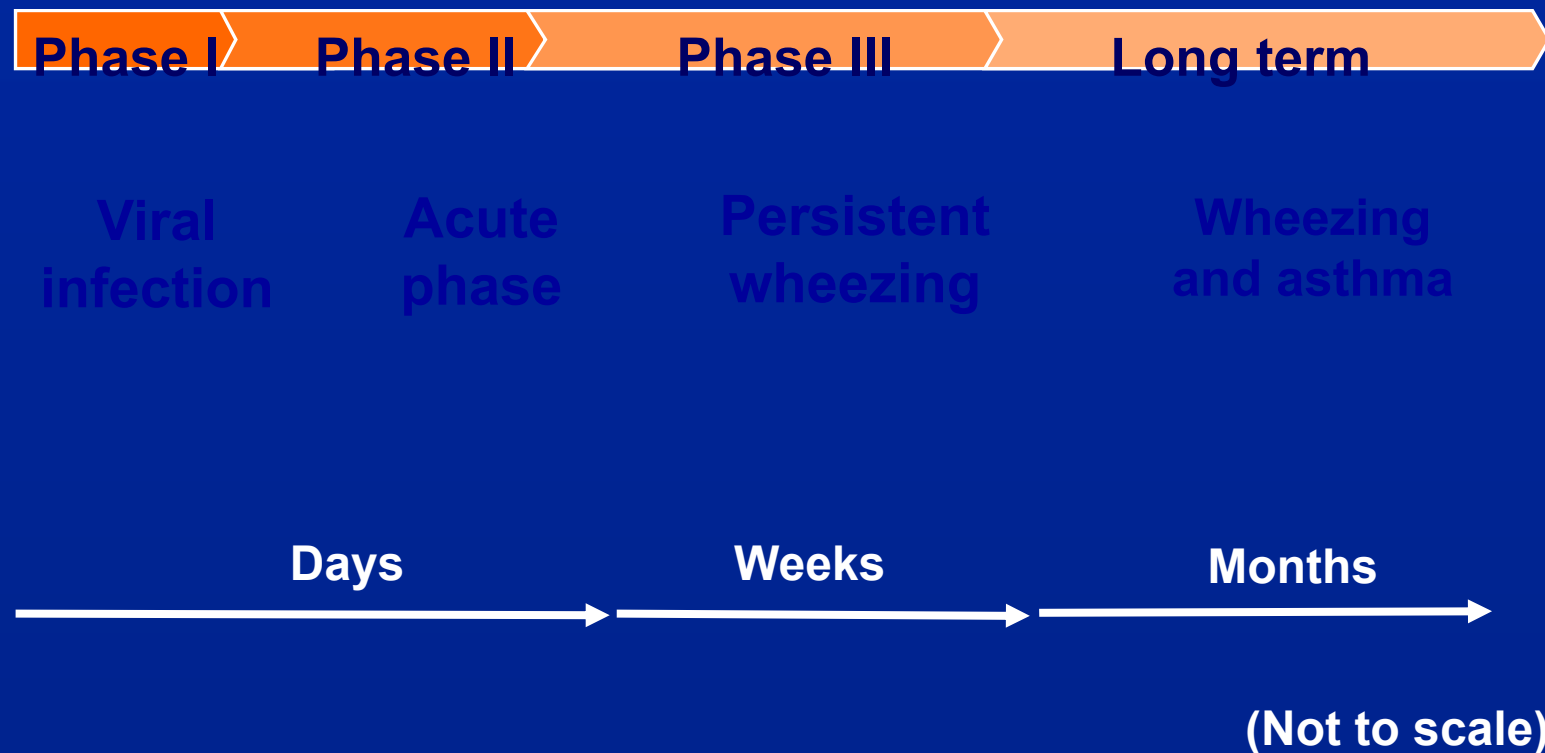


Figure 3.1 Adjusted odds ratios for infrequent and frequent wheeze associated with RSV lower respiratory infections before age 3. (From ref. 18.)

Risk Factors for RSV-Induced Bronchiolitis

- Male
- Aged 3-6 months
- No breast feeding
- Crowded living conditions
- Lower cord serum RSV antibody titre
- Maternal smoking
- Day care attendance
- Born between April and September

RSV-Induced Bronchiolitis May Consist of Several Phases



Bronchodilators (III)

- β 2-agonists do seem to protect against bronchial challenge and to hasten recovery from challenge in infants, suggesting that there are effective β 2-receptors in infant airway smooth muscle.
- The likelihood of a clinical response to β 2-agonists increase with age. This may be explained partly by the greater dose delivered to larger children by some devices.
- Adrenaline; long-acting β 2-agonists; ipratropium bromide

Step 1 (children ≤ 5 years) – as-needed inhaled SABA

