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Asthma Council, 2004

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Algorithm for Asthma Management

1. Patient with asthma presenting with symptoms

2. In acute exacerbation?
   Y → 3. Classify and treat based on Severity Classification of Asthma in Acute Exacerbation*
   N → 4. Currently on controller medications?
       Y → 5. Assess response to current treatment
           Y → 6. Increased or continued need for relievers?
                Y → 7. Step-up controllers
                N → 8. Maintain on current controllers
           N → 9. Spirometry results available?
                Y → 10. Classify using Spirometry results in Classification of Chronic Severity**
                N → 11. Classified as Severe?
                     Y → 12. Treat as Severe Persistent Asthma
                     N → 13. Treat as Mild to Moderate Persistent Asthma
                N → 14. Classify using Symptom Frequency in Classification of Chronic Severity**

15. Asthma symptoms persistent?
    Y → 16. Classified as Severe?
            Y → 17. Treat as Severe Persistent Asthma*
            N → 18. Treat as Intermittent Asthma*
    N → 19. Classified as Severe?
            Y → 18. Treat as Mild to Moderate Persistent Asthma*
            N → 19. Treat as Mild to Moderate Persistent Asthma*

* Refer to Phil Consensus Report on Asthma Diagnosis & Treatment 1996
** Refer to Table 1.3.
Chapter 1

Epidemiology, Diagnosis and Classification of Asthma

Question No. 1: Is asthma a common condition worldwide?

Answer: Yes, asthma is a common disease worldwide and, over the past two decades, is showing an increasing trend for all ages, sex, and racial groups.

Summary of Evidence:
In 1995, the International Study of Asthma and Allergies in Children (ISAAC) conducted Phase I of a worldwide study to describe the prevalence and severity of asthma, rhinitis, and eczema among school children. One hundred fifty five centers in 56 countries participated, including the Philippines. More than 450,000 children were interviewed using a one-page written questionnaire or a video asthma questionnaire. The study showed that the prevalence of asthma symptoms in children varied greatly in different populations with differences ranging between 20- and 60-fold. The highest prevalence was found from centers in the United Kingdom, Australia and New Zealand. Prevalence of asthma is increasing by 4% each year. In the United States, the prevalence of asthma cases was noted to be increasing since the early 1980s for all ages, sex, and racial groups. The prevalence is higher among children than adults and higher among blacks than whites. In the general population, the prevalence of asthma is higher among females, however, in children, the prevalence is higher among males. Furthermore, the prevalence among impoverished inner city children has been much higher.

References:

Question No. 2: How common is asthma in the Philippines?

Answer: There are no available nationwide data published on asthma prevalence. However, the limited reports gathered showed a prevalence of 12% in children aged 13-14 years and 17-22% in older age groups.

Summary of Evidence:
Three thousand two hundred and seven children in Metro Manila aged 13-14 years participated in the ISAAC. Participants accomplished a 12-month prevalence of self-reported asthma symptoms from written questionnaires and from video questionnaires. The results showed that approximately 12% and 8% prevalence based on responses to the written questionnaire and to the video questionnaire respectively. In a subsequent study, 12.3% of the same population reported wheezing. A local study estimating the prevalence of asthma and allergies in adults was completed in Malolos, Bulacan in 1998. One thousand five (1,005) adults (ages 18-44 years) were interviewed using a pre-tested questionnaire adapted from the European Community Health Survey (ECHRS) and the ISAAC. The study showed a prevalence of 17.2% for asthma and 49.9% for allergy among adults. Another study conducted at the Lung Center of the Philippines reported a prevalence of 22% in adults.

References:
Question No. 3:
What is the current concept of asthma as a disease?

Answer:
In the last four decades, asthma was considered as predominantly a disease of airway smooth muscle.\(^1,^2\) However, based on the National Institute of Health (NIH) guidelines in 1997, the understanding of asthma has shifted from a disease of airway smooth muscle to one of airway inflammation.\(^3\) This concept of bronchial inflammation arose from studies of bronchial hyperresponsiveness, bronchoalveolar lavage (BAL), bronchial biopsies and induced sputum from asthmatics, and observations made postmortem of patients who died from asthma.

Interestingly, structural abnormalities in the airways have been observed even on patients maintained on anti-inflammatory medications and on those with mild asthma.\(^4,^5,^6\) Evidently, the incessant release of inflammatory mediators from eosinophils and mast cells results in persistent bronchial inflammation of the airways. Eventually the airways undergo structural abnormalities resulting in the following: fibrosis, increase in mass of smooth muscle and mucus glands,\(^7,^8,^9\) epithelial shedding, thickening of the reticular basement membrane,\(^10\) and fibronectin deposition in the subepithelial layer.\(^11\) Histological sections show thickening of the airway walls by 50-300% of normal.\(^12\) These changes in the composition and organization of the cellular and molecular components of the airway wall result in a process called airway remodeling.\(^13\) Figure 1 shows a proposed mechanism of airway remodeling.\(^14\)

Airway remodeling results in the following physiologic consequences: 1) increase in airway hyperresponsiveness,\(^15,^16\) 2) non-reversibility of airway obstruction and residual obstruction after bronchodilator and anti-inflammatory therapy,\(^3,^16\) and 3) accelerated decline in FEV\(_1\) in a subset of asthmatic patients.\(^14\)

References:
8. O’Hollaren MT. Airway remodeling; where’s the evidence? American College of Allergy, Asthma and Immunology Annual Meeting 1999.
Question No. 4: How is asthma diagnosed?

Answer:
Asthma is diagnosed using a combination of history, clinical findings and objective measurements of variable airflow obstruction and/or bronchial hyperresponsiveness.

However, in some cases, the medical history and physical examination may not be reliable in diagnosing asthma. Furthermore, the physical examination may be normal as asthma symptoms are characteristically episodic. An objective measure is required to diagnose asthma accurately. [GRADE A]

Summary of Evidence:

1. Screening Strategies

A. History

Asthma should be suspected in any patient who presents with any of the following: (1) cough, which worsens at night; (2) wheeze; (3) difficulty in breathing; and (4) chest tightness.1,2 [LEVEL 1] The diagnostic accuracy increases when more than one symptom is present.3 [LEVEL 3] Diagnosis of asthma is strengthened by the presence of the following: history of temporal waxing and waning of symptoms, often provoked by exogenous factors such as allergens, irritants, exercise, and viruses; fever; a positive family history; and improvement in symptoms from use of anti-asthma medications.7

B. Physical Examination

The physical examination of the respiratory system may be normal in patients with asthma. Widespread, high-pitched, musical wheezes are characteristic auscultatory findings; however, they are not very specific for asthma.8,9,10 [LEVEL 1] The presence of wheezes correlates poorly with the severity of airflow limitation. Some patients with asthma may have normal auscultation but exhibit significant airflow obstruction when measured objectively. A better clinical parameter for severity of airflow obstruction is prolonged forced expiratory time of six seconds or more, which correlates well with FEV, in patients with moderate to severe airflow obstruction.11,12 [LEVEL 1]

2. Strategies for Confirmation

A. Forced expiratory volume in 1 second (FEV)

Spirometry is useful in documenting airflow obstruction in asthma. Variable airflow obstruction can be documented by a spontaneous variability in FEV or by improvement 15 minutes after inhaled ß₂-agonist administration. A 12% (at least 200 mL) improvement in FEV, either spontaneously or after inhalation of a ß₂-agonist is considered significant.13,14 [LEVEL 1] A positive test increases the likelihood that a symptomatic patient with baseline airflow obstruction has asthma. If the initial test is not significant, asthma can be diagnosed by demonstrating at least a 20% (minimum of 250 mL) increase in FEV, after one week with or without oral steroids, or after two weeks of inhaled steroids.15,16 [LEVEL 4]

B. Peak Expiratory Flow Rate (PEFR)

In the absence of spirometry, home measurement of peak expiratory flow (PEF), incorporating response to inhaled ß₂-agonist, may be used to document variable airflow obstruction. PEF variability is computed as the mean percentage difference between the post-bronchodilator evening (p.m.) value and pre-bronchodilator morning (a.m.) value over a period of several weeks. Another method is the minimum morning pre-bronchodilator PEF over 1 week expressed as a percent of the recent best (Min%/Max). A PEF variability of 20% or more is indicative of asthma. [LEVEL 4] PEF measurement is also an important diagnostic tool in the clinic, emergency department and hospital. Demonstrating a 20% or greater improvement in PEF over 15 minutes after the administration of 200 to 400 µg inhaled salbutamol or the equivalent may be used as an indicator of asthma.16 [LEVEL 4]

The PEFR correlates closely with the FEV, (r= 0.85).17,18 However, this close correlation speaks more of PEFR as a tool better suited for monitoring rather than for diagnosis. There can be a wide variability when PEFR and FEV are compared directly. PEFR is, therefore, best used as an adjunct to and not as a substitute for spirometry.19 [LEVEL 4]

C. Airway hyperresponsiveness

If asthma is still suspected in subjects with a normal FEV, excessive bronchial hyperresponsiveness can be documented by performing a methacholine or histamine inhalation challenge.20,21 [LEVEL 1] The optimal diagnostic value of these challenge tests occurs when the pretest probability of asthma based on symptoms is 30-70%.22 [LEVEL 2] However, a negative bronchoprovocation test is more reliable in excluding a diagnosis of asthma.23 The test is usually available only in specialized centers with a competent staff. Presently, local guidelines on the performance, dosing, cut-off values, and interpretations have not been established.

References:
6. Sandford, AT, et al. The genetics of asthma.
18. Connelly CK, Chan NS. Relationship between different measurements of respiratory function in asthma. Respiration. 1987;52:22-33.

Question No. 5: How is asthma classified?

Answer:
Asthma can be classified according to: 1) etiology, and 2) severity (clinical condition on presentation whether the patient is in an acute state or in a chronic state).3

A. Etiology
Classification of asthma according to etiology is limited as no environmental cause can be identified. However, a rigorous search for a specific environmental cause should be part of the initial clinical assessment. Identifi-
cation of the specific etiology will guide both the physician and the patient on the use of avoidance strategies in management.

B. Severity

**Acute state (in exacerbation)**

For the physician, the initial step is to recognize decisively if the patient is in acute exacerbation. Such exacerbation can be fatal if not treated appropriately. It is important to emphasize that any patient with chronic asthma, however mild, may have an acute exacerbation. Any patient, even with mild symptoms, should be considered as having an asthma exacerbation if there is: 1) history of life threatening acute attacks; 2) hospitalization within the previous year; 3) psychosocial problems; 4) history of intubation for asthma; 5) recent reductions or cessation of glucocorticosteroid therapy; and 6) noncompliance with recommended medical therapy. These clinical conditions are associated with a higher risk of asthma mortality.

Since acute exacerbation demands an urgent need to intervene and to modify existing treatment, this problem will be discussed in detail separately. (Refer to Chapter 5)

**Chronic State**

Assessment of asthma severity follows the Global Initiative on Asthma classification. Classification of severity is subdivided into four steps: intermittent, mild persistent, moderate persistent, and severe persistent. (See Table 1.2)

Recent publications criticized the GINA classification on severity based on symptoms and frequency of attacks, and PEF and FEV1 values. Long-term mental retention of and adherence to the classification details have not been satisfactory even after intensive dissemination workshops.

Because asthma is a chronic inflammatory disease, the severity of its chronic state exists in a continuum. Numeric cut-off values of frequency and intensity of symptoms, and parameters of physiologic dysfunction currently used to classify asthma in different levels of severity are artificial and transitory. Of note is the fact that the 1994 GINA severity classification, which was recommended in the first Philippine Consensus Report on Asthma Diagnosis and Management (1996), has not been validated.

Table 1.3 shows a revised classification combining mild persistent and moderate persistent categories into one. This new asthma severity classification, beyond its scientific soundness, is more comprehensible and readily applicable to clinical work. [LEVEL 4]

**References:**

4. Garcia HJ. Does a classification of asthma based on its

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**Table 1.2 GINA Classification of Asthma Severity by Clinical Features**

| STEP 1: Intermittent | Symptoms less than once a week  
| Brief exacerbations  
| Nocturnal symptoms not more than twice a month  
| - FEV, or PEF >80% predicted  
| - PEF 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, or PEF > 80% predicted  
| - PEF variability 20-30% |
| STEP 3: Moderate Persistent | Symptoms daily  
| Exacerbations may affect activity and sleep  
| Nocturnal symptoms not more than once a week  
| Daily use of short-acting β2-agonist  
| - FEV, or PEF 60-80% predicted  
| - PEF variability >30% |
| STEP 4: Severe Persistent | Symptoms daily  
| Frequent exacerbations  
| Frequent nocturnal activities  
| Limitation of activities  
| - FEV, or PEF <60% predicted  
| - PEF variability >30% |
Research Recommendations

The wide range in the prevalence rates as reported in the ISAAC and local studies emphasizes the need for a national prevalence survey for asthma.

Classification of asthma severity should be validated.

Chapter 2

Objective Measures in the Diagnosis, Assessment of Severity and Monitoring of Asthma

Question No. 1:
Do clinical symptoms correlate with the degree of airway obstruction?

Answer:
In patients with asthma, clinical symptoms may not always correlate with the degree of airway obstruction. Objective measures of airway obstruction are needed. [GRADE A]

Summary of Evidence:
Asthma symptoms, the visual analog scale and dyspnea scores do not correlate with the level of FEV$_1$ and PEF.$^{1,2}$ [LEVEL 1] In a study by Osborne, a specialist’s assessment of long-term asthma severity did not correlate at all with asthma symptoms.$^3$ Likewise, two separate studies conducted on intra-patient assessment of severity of their own symptoms before and after treatment showed no correlation with FEV$_1$ and PEF.$^{4,5}$ [LEVEL 2]

References:

Question No. 2:
Is peak flow monitoring useful in chronic stable asthma?

Answer:
Yes, peak flow monitoring is useful in chronic stable asthma, especially in patients with moderate to severe persistent asthma. [GRADE C]

Table 1.3 New Classification of Chronic Asthma Severity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Daytime symptoms</td>
<td>Monthly</td>
</tr>
<tr>
<td>Nocturnal awakening</td>
<td>Less than monthly</td>
</tr>
<tr>
<td>Rescue β$_2$-agonist use</td>
<td>Less than weekly</td>
</tr>
<tr>
<td>PEF or FEV$_1$ *</td>
<td>&gt;80% pred.</td>
</tr>
<tr>
<td>Treatment needed to control asthma</td>
<td>Occasional prn</td>
</tr>
<tr>
<td></td>
<td>β$_2$-agonist only</td>
</tr>
</tbody>
</table>

* Objective measures take precedence over subjective complaints. The highest severity level of any domain will be the basis of the final severity level.

** Patients who are high risk for asthma-related deaths are initially classified here.

ICS = inhaled corticosteroid
LABA = long-acting β$_2$-agonist
OCS = oral corticosteroid
Summary of Evidence:
Although clinical trials show conflicting results, evidence suggests that PEFR monitoring improves patient outcome. The Grampian Asthma Study of Integrated Care Trial (GRASSIC) is a randomized controlled trial comparing the effect of PEFR-based self-management against conventional treatment on patient outcome. At the end of a 12-month observation period, the authors showed there was no statistically significant difference in patient outcome between the two groups. However, higher number of physician consultations was seen in the PEFR-based group, reflecting closer monitoring of asthma by the health care professionals. PEFR-based self-management is especially beneficial for patients with severe asthma since it will facilitate closer monitoring by general practitioners and encourage prompt administration of oral steroids whenever appropriate [LEVEL 3].

References:

Question No. 3:
Does peak flow variability correlate with worsening asthma?

Answer:
Yes, and despite the lack of clear evidence to support its use, peak flow variability is a useful indicator of worsening airflow obstruction [GRADE D]

Summary of Evidence:
Population-based studies show that excessive diurnal PEFR variation correlated with a higher incidence of respiratory symptoms, poor asthma control, and sudden death. [LEVEL 2]

Clinical and epidemiological studies have reported good correlation between peak flow variability and the degree of bronchial hyperresponsiveness (BHR) observed after histamine or methacholine inhalation challenge. BHR is currently considered the best available clue to the presence of airway inflammation. Taken together, the available data suggest that PEFR variability is loosely associated with the presence of airway inflammation. This finding is further strengthened by studies that demonstrate improvement in PEFR and decrease in variability after effective control of airway inflammation with inhaled corticosteroids (ICS). [LEVEL 3]

References:

Question No. 4:
Is peak flow monitoring useful in acute exacerbation of asthma?

Answer:
Yes, the measurement of PEFR provides useful information on the severity of asthma attack, response to therapy, need for hospital admission, and risk of early relapse. [LEVEL 2]

Summary of Evidence:
The use of PEF monitoring in the treatment of acute asthma has been shown to reduce unnecessary asthma-related hospital admissions from the emergency department (ED). In studies involving patients treated for acute asthma exacerbation in the ED setting, PEF before and after treatment were taken and compared for admitted and discharged patients. Patients who eventually needed hospitalization have lower PEF both at the beginning and at the end of the ED treatment, indicating a greater severity of airflow obstruction in those who need in-patient care. Other studies suggest that failure of FEV1 or PEF to improve promptly after bronchodilator administration predicts longer ED stay and more frequent need for hospital admission. Thus, available data indicate that individuals showing higher pre-treatment PEFR and an early response to initial bronchodilator administration are less likely to require hospital admission. [LEVEL 2]

References:
2. Kwong T, Town I, Holst PE, et al. A study of the manage-

Research Recommendation
Further local setting studies validating the clinical significance of peak expiratory flow measurements and the predictive value of variability monitoring are needed.

Chapter 3
Control of Triggers
House Dust Mites

Question no. 1: Are house dust mites a significant cause of asthma?
Answer: Worldwide, investigators have found that the dust mite is a significant cause of allergic asthma. [LEVEL 1]

Summary of evidence:
In 1964, mite extracts from house dust were found to produce positive skin reactions. Moreover, patients who had positive bronchoprovocative tests improved when they were removed from contact with mites. These findings led to the conclusion that *Dermatophagoides species* was a principal source of house dust allergens. More recent studies confirmed *Dermatophagoides pteronyssinus* to be the most abundant mite species worldwide. [LEVEL 1]
The allergenic proteins are actually contained in the fecal pellets of the mite. The allergens fall mainly into two immunologically important groups which are clinically relevant to asthma, atopic dermatitis and allergic rhinitis. These allergens persist for months despite eradication of live mites. In investigating for the possibility of exposure, it is best to measure mite allergens in dust vacuumed from surfaces because the fecal pellets remain aerosolized for only a few minutes after they are stirred from a resting place.

References:

Question No. 2:
Are mechanical measures effective in reducing or eradicating house dust mites?

Answer:
Although mechanical removal methods are partly successful in reducing allergens and killing mites, there is no evidence showing long-term improvement in allergy symptoms among sensitized individuals.

Summary of Evidence:
The most effective, and probably the most important avoidance measure is to encase mattresses, pillows, and duvet with covers that are impermeable to mite allergens. By encasing beds and pillows in plastic, dust mite populations were found to be reduced by as much as 75% on both mattresses and surrounding carpets. [LEVEL 1]

Low humidity is an important requirement for dust mite survival. The levels of mite allergens are dramatically reduced at high altitude (>1500 m) where humidity is too low to support mite populations. Theoretically, if relative humidity is kept below 50% for prolonged periods, the mites can be eradicated. Two separate studies showed that mite-sensitive asthmatic children had a progressive reduction in non-specific BHR and a progressive improvement in asthma symptoms when brought to higher altitude environments. Further studies showed a reversal of this trend after 15 days of allergen re-exposure at sea level. [LEVEL 1]

Investigations on the effectiveness of portable dehumidifiers failed to show any reduction in house dust mite population and allergen levels. Another approach in reducing humidity levels is by using mechanical ventilation with a heat recovery unit. This method produced a 100% mite reduction in bedroom mattresses one month after operation and 99.9% reduction after 2 months. Levels of antigen in carpets were found to drop by 86.7% after steam-cleaning or wet cleaning rugs.
To kill mites by washing, the water temperature must be >54.4°C. The dry cleaning process is found to be effective in eliminating mites. One study comparing the effectiveness of dry cleaning with hot-water washing showed that both cleaning methods successfully reduced allergen levels on blankets. Other mechanical measures to eradicate house dust mites remain to be controversial. Use of high efficiency particulate air (HEPA) filters appears to be an insufficient substitute for standard avoidance measures in mite-sensitive patients. Increasing the frequency of vacuuming to at least once per week is controversial because although this practice has shown reduction in mite numbers, the activity may reintroduce allergens to the air.

References:

Question No. 3: Are chemical measures effective in reducing or eradicating house dust mites?

Answer: Currently available chemical products for control of dust mites and their allergens offer only short-term effectivity. [GRADE A]

Summary of Evidence:
Current strategies for mite control frequently employ chemicals that serve to either eradicate the mites or denature the allergens. These chemicals include benzyl benzoate, permethrin, pirimiphos methyl, phenyl salicylate, tannic acid, common household disinfectants, combinations of these, and insect growth regulators. Potential acaricides have had varying degrees of success in both laboratory and clinical trials. However, allergen levels rebounded after two months suggesting that repeated application every two to three months is necessary to control mite allergen levels.

A study by Dietemann and colleagues showed that application of benzyl benzoate in households of asthmatic patients improved their clinical symptoms over a period of one year. However, another study using benzyl benzoate showed that although the mite mortality drop is 100% two months after treatment, this has decreased significantly to 60% by the third month. Phenyl salicylate, a compound structurally similar to benzyl benzoate, was observed to retain its acaricidal activity three months post-application.

Varying degrees of success have been noted with the use of pirimiphos methyl, an organophosphate insecticide, and permethrin, a synthetic pyrethroid. Insect growth regulators (e.g., methoprene and hydropene) act by mimicking normal hormonal activity and significantly suppress mite populations up to 30 days.

Tannic acid, a denaturant capable of breaking down mite fecal allergens, was shown to decrease bronchial hyperreactivity in patients only on the eighth month after treatment of mattress casings and carpets. A major practical disadvantage of using tannic acid is that it stains fabric.

Studies on combined products that employ various concentrations of an acaricide, denaturant and/or fungicide to kill mites and remove allergens had only significant short-term activity ranging from 10-16 weeks post-application.

References:

Question No. 4:
Will patients with asthma who are sensitized to house dust mites benefit from measures designed to reduce their exposure to mite antigen in the home?

Answer: Current methods aimed at reducing exposure to allergens from house dust mites seem to be ineffective and cannot be recommended as prophylactic treatment for asthma patients sensitive to mites [GRADE B]

Summary of Evidence:
A meta-analysis of randomized trials investigated the effects of mite antigen reducing measures on asthma compared to an untreated control group.1 There were 23 studies included, six of which used chemical methods, 13 used physical methods, and four used a combination of both. Altogether, 41/113 patients exposed to treatment interventions improved compared with 38/117 in the control groups leading the investigators to conclude that there is no clinical benefit from measures designed to reduce exposure to mites among asthma mite-sensitive patients. [LEVEL 1] The lack of benefit may be due to failure of the methods used to adequately reduce levels of mite antigen.

Some studies were able to show effective reduction in mite exposure, but these did not show more positive results when compared to studies that failed to reduce mite exposure. This may be because patients with asthma who are sensitive to mites are usually also sensitive to other allergens. Therefore, the successful elimination of only one allergen may be of limited benefit.


Conclusion and Recommendation
House dust mite allergens are significant causes of asthma in mite-sensitive individuals.

Despite the absence of larger and more rigorous studies on methods of mite control, health care givers should continue to institute avoidance and control measures.

Cockroach Allergens

Question No. 1:
Are cockroach allergens an important risk factor for asthma?

Answer: Yes, among the insects, cockroaches are the most recognized common source of allergens [LEVEL 1]

Summary of Evidence:
Cockroaches are tropical in origin and thrive in houses that are continuously warm. However, unlike mites, they are not dependent on ambient humidity and show great talent in finding water sources within a building. Of the seven or eight indoor species, the American cockroach (Periplaneta americana) is the most common cockroach in the Philippines.

Cockroaches can be safely presumed to cause significant asthma in areas where crowded living conditions exist such as urban slums. Socio-economic status and race are independent risk factors for cockroach allergen exposure both in the home and school settings.1,2 There is also a clear dose-response relationship between cockroach allergen exposure and sensitization in children with asthma.3 [LEVEL 1]

References:

Question No. 2:
Are control measures designed to reduce or control levels of cockroach allergens in houses effective?
Answer:
Yes, although obvious allergic reactions to dogs are less common than those to cats. [LEVEL 2]

Summary of Evidence:
From preliminary results of studies, it appears that dog allergens, like cat allergens, also become and remain airborne. Thus, it is likely that the same rules apply to dog allergens as to cat. However, most studies report that children have fewer symptoms as a result of dog allergens than cat allergens: in one study, one in ten reacted to cat allergens, whereas only one in 100 reacted to dog allergens. This despite the fact that more individuals own dogs than cats. However, intimacy of exposure may be a factor – many dogs are kept outside whereas cats more often go into the house and into the bedroom of children. However, in areas where dogs are kept in houses, they can become an important source of allergens. [LEVEL 4]

References:
2. Ingram JM, Sporik R, Rose G, et al. Quantitative as-

Animal Allergens

Question No. 1: Can cat allergens cause asthma?

Answer:
Yes. Cats are a major source of allergen in the home and are capable of inducing symptoms in sensitive patients [LEVEL 1].

Summary of Evidence:
Cat allergens are found in households with cats and have been confirmed to cause asthma in studies using a special cat challenge room. The major cat allergen, Fel d 1, is produced primarily in the sebaceous glands and in the basal squamous epithelial cells of the skin of cats. Very high levels of this allergen were also demonstrated in cat anal secretions. Soft furnishings, carpets and mattresses serve as reservoirs for the allergen. Individuals who have never had a cat may become allergic by exposure to the allergen from contact with cats belonging to others. Furthermore, Fel d 1 has been detected in carpet dust of houses where cats have never been present, suggesting it can be carried into cat-free buildings on the clothing of people exposed to cats.

Because of the small particle size (≤5 mm in diameter) of these allergens, they can be detected in wall surfaces and in the air of undisturbed rooms. This may explain why a sensitized person may experience immediate symptoms when entering a home with a cat, even without direct exposure to the cat.

References:

Question No. 2: Can exposure to dog allergens also cause asthma?

Answer:
Yes, although obvious allergic reactions to dogs are less common than those to cats. [LEVEL 2]

Summary of Evidence:
Dog saliva and dog dander appear to be the main sources of dog allergen (Can f 1). Dog allergen, like cat allergen, can be detected in public places, including schools. Cross-reactivity between dog and cat allergens has been demonstrated, suggesting the presence of common immunologic determinants.

References:

3. ManniAKM, Einerson R, Shou C, et al. Allergens in school dust I. The amount of the major cat (Fel d 1) and dog (Can f 1) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. J. Allergy Clin. Immunol. 1993:91:1067-74.

Question No. 3: Are measures to control cat or dog allergen levels effective?

Answer: There are no existing studies dealing with effectiveness of control measures on cat or dog allergens.

Summary of Evidence: The best way to reduce exposure to cat or dog allergen is to remove the animal from the home. The clinical benefit of control measures in person, who insist on keeping their pets despite continued symptoms has not yet been established. Airborne allergen levels increase by approximately fivefold when the pet is in the room, indicating that the immediate presence of a pet contributes to airborne allergen levels.1

The accepted control measures to control animal allergens are as follows:

1. Remove reservoirs such as carpets and sofas.
2. Keep the cat or dog outside as much as possible.
3. Use room air cleaners (e.g., High-efficiency particulate air cleaner or HEPA), which can reduce allergens if the reservoirs are removed first.
4. Bathe the animal weekly. However, even aggressive washing can only remove about 40 to 70 % of allergens.2,3

References:

Indoor and Outdoor Respiratory Irritants

Question No. 1: Is there a relationship between outdoor air pollution and asthma attacks?

Answer: Yes, outdoor air pollution aggravates asthma. [LEVEL 2]

Summary of Evidence: Several epidemiological studies have shown that of all outdoor pollutants, inhalable particulates ≤10 μm (PM_{10}) in diameter are the single greatest hazard to asthma exacerbation.1,2 Likewise, the peak hourly nitrogen dioxide (NO_{2}) concentrations,3,4,5 increased ozone (O_{3}) and sulfur dioxide (SO_{2}) have individually6,7 or in combination,8 been reported to significantly increase emergency room visit of asthmatics.9,10,11,12,13-15 [LEVEL 2]

Particulate matter (PM) exposure is difficult to achieve in a controlled laboratory setting. However, controlled studies on the effect of sulfuric acid show that asthmatics are more “sensitive” than healthy subjects after exposure.16 High SO_{2} concentration has been associated with short-term increases in morbidity and mortality in the general population during dramatic air population episodes in the past.17 [LEVEL 3] Exposure to concentrations of SO_{2} as low as 0.2 ppm appear to have a significant effect in patients who are mouth-breathing or undergoing heavy exercise. However, these effects are short-lived and not increased by prolonged exposure.18 A combination of low concentration of SO_{2} and NO_{2}—often increased in heavy traffic—has been shown to enhance airway responsiveness to inhaled allergen.19,20

Although controlled clinical trials using ozone are equivocal,21 studies combining allergen challenges after O_{3} exposure showed worsening of atopic asthma.22,23 [LEVEL 3]

Several studies have evaluated the relationship of lung function and exposure to pollutants. In one study, healthy and asthmatic patients were exposed for two hours to 0.40 ppm O_{3} and lung function changes were monitored. Results showed that asthmatic patients have greater PEF decrements and with enhanced reponses to methacholine provocation challenge.24 Other studies showed greater degree of airway inflammation in asthmatics exposed to pollutants25 with higher levels of IL8 and proteins in bronchoalveolar level (BAL) fluid even in the absence of any PEF change.26-31 [LEVEL 3]

In summary, particulate matter exposure is associated with decreased lung function, increased symptoms and unscheduled visits to the emergency room. Exposure to pollutants like SO_{2} causes dramatic bronchoconstriction accompanied by shortness of breath and wheezing in many subjects with asthma. Likewise, such exposure is associated with many signs of asthma aggravation: decreased lung function, airway inflammation, both emergency department visits and hospital admissions, and enhanced response to common aeroallergens. Thus, asthmatics have been shown to be a sensitive population relative to ozone and other air pollutants.

Further researches linking epidemiological, clinical and toxicological approaches are required to better understand and characterize the risk of exposing asthmatics to these pollutants. (See Table 4 on page 53)
References:


20. Rossi OV, Kinnula VL, Tienari J, Huhtei E. Association of severe asthma attacks with weather, pollen and air pollut-


**Question No. 2:**

**Does air pollution cause an increase in asthma prevalence?**

**Answer:**

There is no consistent evidence that common air pollutants are involved in the development of asthma.

**Summary of Evidence:**

Because genetics alone is unlikely to explain the increasing prevalence of asthma worldwide, it is very tempting to attribute the epidemic to environmental factors such as indoor and outdoor air pollution¹.

In many regions of the world, asthma prevalence has increased just as the populations have become westernized.²,³ However, studies comparing asthma and allergy prevalence between highly polluted Leipzig and clean Munich in Germany showed no significant difference between the two westernized cities.⁴,⁵,⁶,⁷ Air pollution may aggravate existing asthma, but it is unlikely to be responsible for the asthma epidemic. [LEVEL 3]

Various studies strongly suggest that air pollution can modulate or enhance airway inflammation associated with allergic and asthmatic diseases. There is now extensive evidence demonstrating adjuvant effects of air pollutants on the formation of specific IgE antibodies and cytokines in both animals and man.⁴,⁵,⁶,⁷
Recommendations

During periods of increased outdoor pollution, asthmatics can minimize exposure by remaining indoors or reducing outdoor physical activities or exercise.

Bronchoconstriction resulting from controlled exposure to air pollutants can be prevented by use of an inhaled bronchodilator. However, continued exposure even with the use of inhaled bronchodilator is unlikely to prevent the inflammatory effects of pollution and may aggravate them by masking symptoms.

Therefore, the primary management approach should be preventing or reducing exposure.

References:

Question No. 3:
Do anti-oxidants confer a protective effect on asthatics exposed to air pollutants?

Answer:
Yes, initial studies show that anti-oxidants may offer some benefit in asthmatic adults exposed to air pollutants [GRADE B].

Summary of Evidence:
Concentrations of antioxidant vitamins in the diet and in the plasma are related to asthma status. Individuals with asthma have been shown to have lower levels of serum antioxidants such as vitamin C and E and β-carotene compared to the general population. [LEVEL 3] In studies evaluating the effect of dietary supplementation with these vitamins on a subject’s response to exposure to ozone, it was shown that patients on vitamin treatment exhibited a lesser BHR than placebo suggesting some benefit in asthmatic adults exposed to air pollutants.

References:

Research Recommendation

More studies are needed before any recommendation can be made on using antioxidants for their protective effect on asthma.
Question No. 4: Can indoor air pollution trigger asthma exacerbation?

Answer:
Yes, indoor air pollution, the most common of which is tobacco smoke, has been shown to definitely increase asthma exacerbation [LEVEL 1].

Summary of Evidence:
There is a significant body of evidence linking tobacco smoke, an indoor pollutant, to asthma exacerbation.1-5 [LEVEL 1] Findings suggest that nitrogen dioxide at concentrations encountered in the home environment can potentiate the specific airway response of patients with mild asthma to inhaled house dust mite allergen.6

Consensus from recent literature reviews and meta-analyses reinforce previous conclusions of health effects of environmental tobacco smoke (ETS) on children.7-10 Although a genetic etiology for asthma is assumed, the development of asthma is considered to be dependent on environmental factors, such as exposure to allergens including ETS. This exposure may cause asthma onset in children and adults and early non-allergic wheezing in infants and children. It also increases the frequency and severity of symptoms among those with established disease.10,11,12

Environmental tobacco smoke exposure is thus an accepted risk condition for pulmonary and other diseases.

References:

Research Recommendation
More research is necessary to clarify the pathologic mechanisms by which environmental tobacco smoke causes or aggravates asthma.

Infections and Asthma Development

Question No. 1: Is there an association between respiratory infections and the development of asthma?

Answer:
Yes, there is emerging evidence that infections early in life (i.e., in utero and in early infancy) have profound influence on the development of asthma in later life. [LEVEL 2]

Summary of Evidence:
Since asthma is an inflammatory disease,1 the main immunoglobulin implicated (IgE) and the kind of inflammatory cytokines predominating (IL-4, IL-5, IL-13) point to a predominance of the TH2 response.2 TH2 helper lymphocyte-2 response is further characterized by increased production of IFN-γ and Il-4 level-12.3 It is now known that the intrauterine milieu is skewed towards the TH2 phenotype. The most vulnerable period for the switch from TH1 to TH2 is during pregnancy and early infancy.4,5 Some viral infections like the RSV6,7 and EBV8,9 favor the TH2 responses and has been associated with increased allergen sensitization in later life.10-12 Respiratory Syncitial virus infection has been associated with increased Epstein Barr virus in children regardless of asthma history.14,15,16

On the other hand, absence of the more common infections (Mycobacterium tuberculosis,17 measles,18 Hepatitis A,19 other respiratory viruses20 and helminthic infestations) during early childhood impairs the drive to maturation of the TH, pathway,21 causing a relative increase in TH1. This phenomenon is believed responsible, at least in part, for the higher prevalence of asthma in families with fewer siblings, in affluent societies, and in the western, industrialized world. These conditions, resulting in a cleaner environment, avert exposure to and development of common childhood infections.21,22 However, in these same conditions, the prevalence of asthma and other atopic diseases, which were considered rare a few decades ago, appear to have doubled every 10-15 years, with the highest prevalence rates seen in the industrialized western world.23

References:
1. Guidelines for the Diagnosis and Management of Asthma:


Question No. 2:
Is there an association between tuberculosis infections and the development of asthma?

Answer:
Existing data show that asthma is less likely to occur in tuberculin skin test (PPD) positive patients. [LEVEL 2]

Summary of Evidence:
The association of asthma and tuberculosis (TB) is not as easy to explain. In a study among 867 Japanese school children aged 12-13 years, asthmatic symptoms were one half to one third less likely in positive tuberculin responders as in negative responders. Remission of atopic symptoms between the ages of 7 and 12 years was 6-9 times more likely in positive tuberculin responders. In the investigation of this possible association, it was established that the positive tuberculin responders had significantly lower levels of the TH1 cytokines IL-4, IL-10, and IL-13 and higher levels of the TH2 cytokine IFN-γ.1 Apparently, this ability to stimulate TH2 response suppresses TH1 sensitization which, in turn, curbs the inflammatory cascade in asthma. Therefore, asthmatic subjects may be tuberculin negative although not necessarily uninfected since the skin test reaction is just being naturally suppressed in the asthmatic TH1 phenotype.2,3

Aside from tuberculin reactivity, other indicators appear to prove the purported protection. In one study, the asthma prevalence established with the ISAAC project was correlated with the WHO data on smear-positive tuberculosis (TB) cases in countries where TB information was deemed reliable. There were less questionnaire-based asthma cases wherever active TB prevalence was high.4 Furthermore, there was low asthma occurrence among children in high TB prevalence areas which may indeed be indicative of asthma protection from M. TB infection.

References:
1. Shirakawa T, Enomoto T, Shimazu S, Hopkin J. The inverse association between tuberculin responses and atopic
dose of salbutamol used in nebulization. Most likely due to the relatively higher incidence of tremors and palpitations in the intravenous treated group. Decreases in serum potassium were noted more often in the nebulized group, with a higher response rates in the nebulized group.

**Question No. 3:**
Is there an association between respiratory infections and acute exacerbations of asthma?

**Answer:**
Yes. Respiratory infections have been shown to trigger asthma exacerbations. [LEVEL 1]

**Summary of Evidence:**
Respiratory infections are among the most common triggers for asthma exacerbations. It seems that once asthma is established, re-exposure to most infections tend to disturb the airway, inducing more symptoms and, in many cases, frank exacerbation. Routine antibiotic use is not justified since most infections are viral and self-limiting. Sputum purulence may just reflect eosinophilia and does not by itself justify antibiotic use.

**References:**

**Chapter 4**

**Inhalational Devices**

**Question no. 1:**
Is the inhalational route preferred over systemic administration of asthma medications?

**Answer:**
Yes, inhalational route is preferred over systemic administration [GRADE A].

**Summary of Evidence:**
The effects of nebulized and intravenous salbutamol in severe and acute asthma were compared in two separate studies. Both studies demonstrated better and faster response rates in the nebulized group. [LEVEL 1] Decreases in serum potassium were noted more often in the intravenous treated group. However, there was a higher incidence of tremors and palpitations in the nebulized group, most likely due to the relatively higher dose of salbutamol used in nebulization. [LEVEL 2] Nebulized salbutamol was likewise compared with subcutaneous epinephrine in children with acute attacks. There were no differences noted in the clinical, physiologic and pulmonary parameters measured in both treatment arms. However, there were more reports of nausea, vomiting, tremors, headaches, palpitations, excitement and pallor in the subcutaneous group.

**References:**

**Question No. 2:**
Is there a difference among the various inhalational devices in terms of drug deposition, efficacy, safety and promotion of compliance?

**Answer:**
There is no clear evidence that any one device is superior over the other. Although lung deposition studies show superiority of some inhaler devices, it is not clear whether this translates to improved efficacy [LEVEL 2].

**Summary of Evidence:**
The pressurized metered dose inhaler (pMDI), when used with optimal technique, delivers about 10-20% of the nominal per puff dose to the targeted airways. In normal patients, lung deposition with directly labeled salbutamol can reach from 21.6 +/- 8.9% while patients with reversible airflow obstruction achieve lung deposition of 18.2 +/- 7.8%. [LEVEL 2]

Certain maneuvers appear to improve lung deposition. Lung deposition was 18.7% when inhaling from residual volume and 33% when inhaling from 50% of vital capacity. [LEVEL 5] Use of spacers increased the amount of drug deposited in the airways in both normal and asthmatic patients (12.4 +/- 3.5% and 19.0 +/- 8.9%, respectively) possibly because spacers act to condition the aerosol, slowing the jet of medication and allowing the propellant to evaporate. In another study on mild to moderate asthma, use of a spacer device increased lung deposition to 44.1 +/- 10.1%. [LEVEL 2] In comparison, single dose dry powder inhalers (DPIs) show lung deposition between 9.1 and 12.4% whereas the Diskus delivers about half of that to the lungs with about 1.28 fold difference. [LEVEL 2]

Regardless of the significant differences in lung deposition among the inhaler devices, it is not clear whether these differences are clinically important. For broncho-
ilators, especially, only a very small amount of the drug is needed to produce a useful clinical effect. In a Cochrane Review on "Pressurized Metered Dose Inhalers versus All other Handheld Inhalers Devices to Deliver \( \beta_2 \)-agonists Bronchodilators for Non-acute asthma", results show that there were no differences between devices for most clinical outcomes.\(^9\) [LEVEL 1]

In any inhaler device used in the treatment of asthma, systemic adverse events may be expected from the drug being absorbed from the lung or from the gastrointestinal tract. In a study on normal subjects treated with inhaled beclomethasone, sytemic activity was greater using a DPI (52\%) than using a MDI with a large volume spacer (28\%).\(^10\) For the two commonly prescribed dry powder inhalers, systemic bioavailability was higher for budesonide via Turbuhaler (39\%) compared to fluticasone via Diskus (13\%), however, plasma cortisol levels did not differ significantly between the two groups. [LEVEL 2]

References:


Question No. 3:
Is wet nebulization better than other inhalational delivery devices in the acute care setting?

Answer:
No. Wet nebulization is not any better than other inhalational delivery devices in the acute care setting. In fact, the use of a metered-dose inhaler (MDI) with or without a chamber (valve spacer device) is preferred over the use of a wet nebulizer for patients with mild to moderate asthma. A spacer device is recommended whenever the MDI is used for severe asthma [GRADE A].

Summary of Evidence:
Three randomized, double-blind studies compared the efficacy of salbutamol administered either by nebulization (NEB) or by MDI with a spacer in adults with moderate to severe acute astmatic attacks.\(^1\) All studies consistently demonstrated that NEB and MDI are equally efficacious in improving FEV\(_1\), PEFR and clinical symptoms. [LEVEL 1] However the NEB group reported more headaches, palpitations, tremors\(^3\) and anxiety\(^1\). In another randomized open design trial, the use of NEB, MDI and dry powder was evaluated in acute severe asthma in adults. The three delivery systems were found to improve FEV\(_1\) similarly. [LEVEL 1] No evidence of cardiovascular adverse events were seen.\(^4\)

Two studies involving children compared the effects of NEB and MDI in mild\(^4\) and severe\(^4\) acute asthma. In both studies, FEV\(_1\) was shown to improve with both devices. However the improvement in FEV\(_1\) was higher in the severe attack group using the MDI. [LEVEL 2] The NEB group had higher heart rates, while the MDI group reported more dryness of mouth, throat irritation and more coughing. Despite these side effects, most of the children preferred MDI over the NEB because of its shorter administration time.

References:

Answer: Inhaled \( \beta_2 \)-agonists, due to their rapid onset of action, are recommended as first line therapy in the management of acute asthma [GRADE A].

Summary of Evidence:
Inhaled short-acting \( \beta_2 \)-agonists are the drugs of choice for the initial management of acute exacerbations of asthma. They are effective bronchodilators [LEVEL 1] and have the fewest side effects. The minimum dose of short-acting \( \beta_2 \)-agonists that will effectively control asthma symptoms should be used\(^2\) and they should be used on an as-needed (not regular) basis. [LEVEL 2]

References:

Question No. 3:
Does systemically administered \( \beta_2 \)-agonists have a role in acute asthma exacerbations?

Answer:
No, there is no evidence to support the use of intravenously administered \( \beta_2 \)-agonists in acute asthma exacerbations [GRADE A].

Summary of Evidence:
A meta-analysis addressing the issue on the advantages using intravenous (IV) \( \beta_2 \)-agonists in acute asthma exacerbations was recently published by Travers et al. In this review, 15 randomized clinical trials spanning a period of 25 years involving 584 patients were analyzed. The authors concluded that the use of IV \( \beta_2 \)-agonists, either as an adjunct to, or a replacement of, inhaled bronchodilator therapy appears to offer no clinical benefit in acute asthma. [LEVEL 1]

Other issues, however were not addressed in this meta-analysis are:
1. Benefit of IV therapy in ventilated patients
2. Efficacy in the pediatric population since there were very few pediatric clinical trials identified
3. The efficacy of IV \( \beta_2 \)-agonists in patients who are unable to use inhaled \( \beta_2 \)-agonists
4. The administration of \( \beta_2 \)-agonists via subcutaneous route

Reference:

Question No. 4:
Should intravenous aminophylline be used as first line drug for acute asthma?

Answer:
No, intravenous aminophylline should not be used as a first line for the treatment of acute asthma. [GRADE A]

Summary of Evidence:
Intravenous aminophylline offers little benefit over \( \beta_2 \)-agonist in the treatment of acute asthma.\(^1\) In a study assessing the role of aminophylline in adults, 44 asthmatics were initially treated with nebulized \( \beta_2 \)-agonist, then randomized to receive either an infusion of aminophylline or placebo if their peak flow rates did not improve to more than 40% predicted.\(^2\) For both groups, nebulized \( \beta_2 \)-agonist was continued and intravenous methylprednisolone was started. There was no clinical benefit observed in the aminophylline group over the placebo group. Furthermore, higher incidence of side effects was noted in the aminophylline group. [LEVEL 2]

Systematic reviews evaluating randomized controlled
trials of aminophylline compared to placebo in the acute treatment of adults and children clearly demonstrate a lack of benefit in major outcomes such as pulmonary functions and admission rates. [LEVEL 1] These studies also identified excessive side effects which outweighed the benefits of aminophylline in this setting.

Currently, aminophylline can only be used as an option for patients where all other modalities had failed (β₂-agonists, corticosteroids, ipratropium bromide, magnesium, oxygen, IV salbutamol, etc.) and even then should be used cautiously.⁷,⁸

References:

Question No. 5:
Should systemic steroids be used in acute exacerbations of asthma?

Answer:
Yes. The use of short course systemic steroids has been shown to shorten duration of attacks, prevent relapse in the outpatient treatment of asthma exacerbations and reduce subsequent hospital admissions [GRADE A].

Summary of Evidence:
A meta-analysis of studies on systemic steroids clearly shows the benefit of systemic steroids in patients with asthma exacerbation. [LEVEL 1] This review suggests that the early administration of corticosteroids may reduce rates of admissions to the hospital. The treatment appears to be most effective in patients who have severe asthma and who have not received inhaled corticosteroids during their initial presentation.

Use of corticosteroids in acute asthma is effective not only in reducing hospital admission rates, but also in improving pulmonary function, and reducing relapses of asthma.⁴ Since it is difficult to predict which patients will improve spontaneously, corticosteroids should be offered to every patient who presents with an acute exacerbation of asthma.

References:

Question No. 6:
In the treatment of acute exacerbations, are oral steroids as effective as parenteral steroids?

Answer:
Yes, oral steroids are just as effective as parenteral steroids [GRADE A].

Summary of Evidence:
The onset of effect in pulmonary function occurs within three hours and reaches a peak effect within 8 to 12 hours following a single dose of oral prednisolone. Following intravenous prednisolone, the effect on pulmonary function can be measured after 60 minutes, with maximal improvement occurring in about 5 hours. However, comparative studies have not shown a significant benefit of IV over oral administration in the initial treatment of severe asthma. In fact, systematic reviews show that oral steroids are just as effective as IV steroids in controlling acute asthma. Based on these findings, it is recommended that corticosteroids be administered early and by mouth; intravenous treatment should be reserved for those who cannot tolerate food intake.

References:

Question No. 7:
What is the effective dose of corticosteroids for acute asthma?

Answer:
The recommended dosage is hydrocortisone 50 mg four-times-a-day for 48 hours, followed by oral prednisone. [GRADE A]
Summary of Evidence:

Twelve controlled clinical trials examined the dose-response effect of corticosteroids. Of these, only 2 studies were able to show a difference between doses.¹

[LEVEL 1]

Generally, the literature does not support the use of high dose corticosteroids in acute asthma. Hydrocortisone 50 mg four-times-a-day for 48 hours, followed by oral prednisone, was as effective as 200 mg or 500 mg of hydrocortisone followed by high dose prednisone.²³ The effective dose of oral prednisolone was established to be between 30-50 mg daily.¹ Furthermore, the use of high doses of steroids are associated with increased adverse effects, such as mood disturbance and myopathy.³

References:


Question No. 8:
What is the recommended dose interval for oral steroids?

Answer:
The recommended dose interval of oral steroids is every 12 hours. [GRADE A]

Summary of Evidence:

Since the duration of action of corticosteroids on lung function in unstable asthma is 9 hrs, oral steroids should be given every 12 hours.¹² One study suggests a decline in the efficacy of steroids over 7-12 hours, so four-times-a-day dosing is suggested until the FEV₁/PEFR is 50-60% of predicted, when the dose may be decreased and given twice a day.³

References:


Question No. 9:
What is the role of ipratropium bromide in the management of acute asthma?

Answer:
The use of ipratropium bromide alone for acute asthma has been shown to be inferior to β₂-agonists in terms of bronchodilating properties. The addition of nebulized ipratropium bromide to salbutamol, however, further improves the FEV₁ or PEFR in the initial treatment of acute asthma attacks [GRADE A].

Summary of Evidence:

A pooled analysis of three randomized double-blinded clinical trials conducted in the United States, Canada, and New Zealand involving 1,064 patients (18-55 yrs), clearly demonstrated that the addition of ipratropium to salbutamol in the treatment of acute asthma produces a small improvement in lung function, and reduces the risk of the need for additional treatment, subsequent asthma exacerbations, and hospitalizations.¹

A meta-analysis of ten randomized, placebo-controlled, double blinded trials involving 1,377 patients (>18 yrs) showed a modest but statistically significant improvement in airway obstruction (improvement of FEV₁, by 100 mL or a PEFR improvement by 31.5 L/min) among patients who were given a combination of ipratropium bromide plus salbutamol; (either in metered dose or wet nebulization). However, the clinical significance of this improvement remains unclear. It is interesting to note that none of the trials analyzed reported serious adverse effects attributable to either the combination therapy or the single-therapy regimen.² [LEVEL 1]

A smaller randomized, double-blinded clinical trial involving 180 patients compared the effect of salbutamol plus placebo with ipratropium bromide plus salbutamol at higher doses, using metered dose inhaler and spacers at 10-minute intervals for three hours (24 puffs or 2880 µg of salbutamol and 504 µg of ipratropium bromide each hour). The results of this study showed that there may be substantial therapeutic benefit from the addition of ipratropium bromide to salbutamol administered in high doses through MDI plus spacer, particularly in patients with FEV₁ less than 30% and with long duration of symptoms before presentation at the Emergency Department.³ [LEVEL 2]

References:


Research Recommendation

Further studies are needed to determine if the initial use of combined ipratropium bromide and a β₂-agonist will cause significant clinical improvement in terms of patient’s symptom relief, duration of stay in the Emergency Department (ED), and the probability of hospitalization.
Chapter 6

Chronic Management of Asthma

Controller Medications

Question No. 1:
Are inhaled corticosteroids effective in the chronic management of asthma?

Answer:
Yes. Inhaled corticosteroids (ICS) are the mainstay therapy for persistent asthma [GRADE A].

Summary of Evidence:
Long-term treatment with inhaled corticosteroids suppresses the disease by affecting the underlying airway inflammation. Several studies demonstrate that inhaled corticosteroids are effective in reducing symptoms and exacerbations, improving lung function, and decreasing the need for bronchodilator rescue therapy.\(^1,2\) A reduction of airway inflammation, manifested both by airway histology findings and improved airway hyper-responsiveness (AHR), has also been documented.\(^3,4,5,6\) [LEVEL 1]

The outcome parameter responding most rapidly to the initiation of inhaled corticosteroids is symptom relief. The PEF values improve more gradually, while improvements in AHR may continue over many months or even years.\(^1,3,7\)

References:

Question No. 2:
Does early intervention with inhaled corticosteroids result in a better outcome?

Answer:
Yes. Anti-inflammatory therapy, specifically inhaled corticosteroids when started early in the course of asthma, diminishes the adverse effects of airway inflammation [GRADE A].

Summary of Evidence:
Long standing uncontrolled asthma is associated with lower levels of lung function, greater airway hyperreactivity, more symptoms and greater use of \(\beta_2\)-agonists.\(^1\) Lung function in uncontrolled asthma deteriorates progressively over time and leads to irreversible obstruction in 80% of elderly patients.\(^2\) The decrease in FEV\(_1\), among asthmatics is 38 mL/year, compared with 22 mL/year in non-asthmatics. Delay in initiating therapy with inhaled steroids for as little as two years, is associated with a blunted improvement in lung function (FEV\(_1\)) when compared with patients treated with inhaled corticosteroids one to two years earlier.\(^3\) Patients with symptoms of asthma for less than two years prior to initiation of inhaled corticosteroids had higher mean FEV\(_1\) and PEF values than those who had symptoms for a longer period of time prior to initiation of inhaled corticosteroid therapy.\(^4\) These studies suggest that inhaled corticosteroid therapy, in addition to suppressing the disease, may also modify the disease outcome if prescribed early enough and given long enough.\(^3,5,6\) [LEVEL 1]

References:

Question No. 3:
Are inhaled steroids safe in the chronic management of asthma?

Answer:
Yes. Anti-inflammatory therapy, specifically inhaled corticosteroids, when prescribed early and given long enough, diminishes the adverse effects of airway inflammation [GRADE A].

Summary of Evidence:
Long standing uncontrolled asthma is associated with lower levels of lung function, greater airway hyperreactivity, more symptoms and greater use of \(\beta_2\)-agonists.\(^1\) Lung function in uncontrolled asthma deteriorates progressively over time and leads to irreversible obstruction in 80% of elderly patients.\(^2\) The decrease in FEV\(_1\), among asthmatics is 38 mL/year, compared with 22 mL/year in non-asthmatics. Delay in initiating therapy with inhaled steroids for as little as two years, is associated with a blunted improvement in lung function (FEV\(_1\)) when compared with patients treated with inhaled corticosteroids one to two years earlier.\(^3\) Patients with symptoms of asthma for less than two years prior to initiation of inhaled corticosteroids had higher mean FEV\(_1\) and PEF values than those who had symptoms for a longer period of time prior to initiation of inhaled corticosteroid therapy.\(^4\) These studies suggest that inhaled corticosteroid therapy, in addition to suppressing the disease, may also modify the disease outcome if prescribed early enough and given long enough.\(^3,5,6\) [LEVEL 1]

References:
of asthma?

Answer: Yes, inhaled steroids are relatively safe. At low to moderate doses, inhaled steroids do not frequently exhibit clinically important side effects and provide asthmatics a good risk-benefit profile [GRADE A].

Summary of Evidence:
The occurrence and magnitude of adrenal suppression is the most extensively studied systemic effect of inhaled corticosteroids. However, even if moderate and high doses of exogenous corticosteroids affect the hypothalamic-pituitary-adrenal (HPA) axis, the resulting adrenal suppression does not appear to be clinically important, as there were no cases of adrenal crisis reported in adults using only inhaled corticosteroids. [LEVEL 3] In children, only two such cases have been reported, each patient having received 400 and 1000 µg of budesonide for several years.1

In patients reporting any bony abnormality from inhaled steroid use, a causal link between the abnormality found and inhaled therapy is often impossible to prove.2 Many such patients would have previously received short- or long-term therapy with oral steroids, which in turn would likely to have effects on bone turnover with resultant structural abnormalities. Even in studies involving patients who have never received exogenous steroids, the bone mineral density (BMD) results are conflicting. Moreover, severe asthma may in itself affect BMD through its effect on the lifestyle of the patient (e.g. less exercise, different dietary habits).

Data on the causal relationship between ICS use and development of cataracts and glaucoma also show conflicting results. Currently available data suggest that the risk of developing posterior subcapsular cataract is not increased in patients being treated with inhaled corticosteroids alone, even when high doses (up to as mean dose of 1,500 µg/day) were used for a mean of nine years of treatment.3 A more recent epidemiologic study conducted in Canada suggested that patients aged 66 and older receiving high-dose inhaled corticosteroids (1,500 µg/day) continuously for at least three months have an increased risk of glaucoma (odds ratio 1.4, CI 1.1-3.0).4 [LEVEL 3] This observation needs further assessment in controlled, preferably prospective studies.

Thinning skins and easy bruisability are unwanted effects that occur in a dose-dependent fashion with inhaled corticosteroids. It appears to have a higher prevalence in older female patients.5,6 The effects are due to a reduction in extracellular ground substance in the dermis possibly because of reduced dermal fibroblast activity. The effects are very rarely seen when total daily doses of inhaled corticosteroid are less than 1,000 µg. [LEVEL 3]

Oral candidiasis, or thrush, has been reported in up to 5% of adult patients receiving inhaled corticosteroids. When it occurs this can be easily managed by nystatin mouthwash. The risk of occurrence can be greatly reduced by mouth rinsing with water immediately after inhalation, or with the use of a spacer device (with a MDI) or Turbuhaler.7 Dysphonia, or nonspecific throat symptoms are reported to occur in up to 58% of patients taking inhaled corticosteroids via MDI.8 These effects were not diminished by the use of spacer devices. However, in studies using the Turbuhaler, the prevalence of this local side effect appears to be lower,9 probably owing to the different position of the vocal cords during the inhalation process.

References:

Question No. 4:

Does the addition of long-acting bronchodilator to inhaled corticosteroid produce better control of asthma than corticosteroid alone?

Answer: Yes, combining a long-acting inhaled β2-agonist like salmeterol or formoterol with inhaled corticosteroids leads to greater improvement in the control of symptoms and lung function among patients with persistent asthma [GRADE A].

Summary of Evidence:
This recommendation is based upon the results of two
landmark placebo-controlled clinical studies. Greening et al. compared the effect of adding 50 μg of salmeterol with doubling the steroid dose in asthmatics who remain symptomatic despite maintenance treatment with low dose inhaled beclomethasone dipropionate (BDP) at 400 μg. This study showed that the increase in mean morning PEF was greater when salmeterol was added than when BDP dose was doubled.1 [LEVEL 1] Woolcock et al. performed a similar study on asthmatics using higher doses of BDP. Compared to doubling the dose of BDP, the addition of salmeterol to moderate doses of BDP improved lung function and increased the number of symptom-free days.2 [LEVEL 1] These two studies clearly demonstrate that regular, long-acting β2-agonist therapy improves lung function in patients already on inhaled glucocorticoids.

Subsequent studies3,4 strengthen further the conclusion that, in patients not ideally controlled on moderate doses of inhaled steroids, the best clinical decision is to add a long-acting β2-agonist. However, fears have been raised about the effects of regular treatment with long-acting β2-agonists on tolerance or its ability to mask an increase in airway inflammation because of the lower doses of inhaled corticosteroids used. This concern was addressed adequately in the Formoterol and Corticosteroid Establishing Therapy (FACET) study.5 The FACET study has shown that inhaled formoterol and budesonide have independent effects on asthma exacerbation rates and that formoterol improves lung function. Furthermore, these effects were maintained over the entire one-year study period with no adverse safety implications. Regular treatment with formoterol combined with budesonide did not cause any long-term loss of control of asthma. Previous studies did show that there were no signs of worsening of disease or tolerance to the effects of long-acting β2-agonist (LABA) with regard to any clinical or functional variable examined.6,9 [LEVEL 1]

References:

Question No. 5:
Is there a role for fixed dose combination therapy (long-acting β2-agonist and inhaled corticosteroids) in the management of persistent asthma?

Answer:
Yes, recent studies suggest that additional clinical benefit can be achieved with fixed dose combination therapy of LABA and ICS [GRADE A].

Summary of Evidence:
Numerous researches, all randomized, double-blind, placebo-controlled and parallel group design compared the effects of the fixed combination therapy of salmeterol and fluticasone to either steroid alone (either BDP, budesonide or fluticasone), salmeterol alone and placebo. These studies unequivocally demonstrated that addition of an inhaled LABA to the ICS treatment improves all aspects of asthma control.1,2,3,4 [LEVEL 1]

The additional clinical benefit derived from the fixed-combination therapy results not only from the LABA-glucocorticoid interaction but also from the steroid-induced transcription of β2-adrenoceptor gene with the resultant increased synthesis of the β2-receptor protein. This interaction between the LABA and the ICS increased the efficacy of both drugs. Fixed dose combination therapy has likewise been found to be beneficial in terms of other aspects of asthma management such as cost of treatment1 and patient compliance.5,6,7,8,9 [LEVEL 2]

References:
5. van den Berg NJ, et al. Salmeterol/fluticasone propionate
Yes, theophylline has a role in the management of chronic asthma, but because of its low bronchodilating effect and potential for significant adverse effects, it should not be used as first line therapy [GRADE B].

Summary of Evidence:
Theophylline is a commonly prescribed bronchodilator therapy, preferred by some physicians because of the oral administration and relatively low cost.

Recent studies indicate that theophylline, when added to a medium dose or low dose of inhaled steroids (Budesonide (BUD) 800 µg/day or BDP 400 µg/day), was more effective in controlling asthma than doubling the inhaled steroid dose.\(^1,2\) [LEVEL 3] Theophylline was also found to be useful for the control of nocturnal asthma because it improved airflow during the early hours of the morning and reduced bronchial hyperreactivity.\(^3,4\) It was effective when given as a nocturnal slow-release (SR) preparation in patients with nocturnal asthma and when wheezing is not responsive to inhaled long-acting \(\beta_2\)-agonists. [LEVEL 2]

Recent evidence shows that theophylline improves lung function at serum levels below the accepted therapeutic range (<10 mg/L) in patients with moderate asthma who are already on high dose inhaled steroids.\(^5,6\) [LEVEL 3] Furthermore, withdrawal of theophylline from an asthma regimen results in an increase in asthmatic symptoms and a need for higher dose of oral steroids.\(^7\) In one study, theophylline was found to be as effective as beclomethasone even when serum theophylline concentrations were lower than traditional levels of normal therapeutic range for bronchodilation.\(^8\)

Theophylline was also found to exhibit anti-inflammatory effects. In patients with atopic asthma given an allergen challenge, theophylline appeared to inhibit the late response to allergen and cause a reduction in bronchial mucosal eosinophils.\(^9\) [LEVEL 3]

Common adverse effects of theophylline include nausea, vomiting, and other gastrointestinal symptoms. Cardio-pulmonary effects include tachycardia, arrhythmias, and occasionally, stimulation of respiratory center. Appropriate dosing and monitoring can generally avoid these. A general approach is to aim for a steady state serum concentration of between 5-15 µg/mL. Previous studies have shown that theophylline levels of 8.7 µg/mL were achieved in patients given slow-release theophylline in a dose of 500-750 mg/day.\(^1\)

Doxofylline is a newer xanthine derivative with claims of equivalent bronchodilating property and less side effects.\(^11,12\) However, there is very little available evidence to support this. Data to support its anti-inflammatory effects is likewise lacking.

References:
addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur Respir J. 1997;10:2754-60.


Question No. 8: What is the role of anti-leukotrienes in asthma treatment?

Answer: Anti-leukotrienes (Anti-LTs) or leukotriene-receptor antagonists (LTRAs) may be given as a controller drug for mild persistent asthma whenever inhaled corticosteroid (ICS) are not in use. [GRADE A]

For moderate to severe persistent asthma, they may be used as an add-on therapy. [GRADE B]

Summary of Evidence: Studies comparing anti-LTs and ICS consistently show the latter to be the more potent controller.1,2 [LEVEL 2] However, there were some non-ICS-responders who showed significant improvement with anti-LTs. Furthermore, some patients clearly preferred anti-LTs over ICS due to the greater improvement of lung function associated with the steroid.3 The oral formulation and the positive feedback of symptom relief argue for the use of the anti-LTs as first-line controller therapy. Therefore, under selected circumstances, particularly when inhaled corticosteroids are not available or the patient refuses to take ICS, the anti-LTs would be suitable first-line or substitute controllers. [LEVEL 4]

Among patients already on low or high dose inhaled steroids and who are still symptomatic, the addition of anti-LTs provides for additional control.4-8 Several studies show that asthma symptoms and lung function improved, and that frequency of exacerbations were significantly reduced. Furthermore, the use of anti-LT can facilitate dose reduction of the maintenance inhaled and/or oral steroids.9,10,11 [LEVEL 2]

References:


Question No. 9: Are anti-leukotrienes comparable with the currently available add-on controllers?

Answer: Anti-LTs have less bronchodilating effect and symptom relief compared to inhaled long acting bronchodilators1 [LEVEL 1] but have similar effects compared to theophylline. [LEVEL 4]. However, anti-LTs have greater anti-inflammatory activity over both LABA and theophylline. [LEVEL 2]

Summary of Evidence: The addition of either anti-LTs or LABA to inhaled steroids as maintenance therapy has resulted in less...
asthma symptoms, better quality of life and fewer exacerbations.\textsuperscript{1,2,4,5,6} \textbf{[LEVEL 1]} In a study comparing montelukast and salmeterol as add-on therapy in subjects on concurrent ICS, there was no difference in asthma exacerbation and adverse reaction rates. Before and after within group analysis, nonetheless, showed that both treatments are equally effective.\textsuperscript{7} \textbf{[LEVEL 3]}

In a double blind randomized study involving 197 patients with mild exercise-induced bronchospasm (EIB), wherein 25\% of the subjects were on concurrent ICS, salmeterol protection waned significantly more than montelukast by the 4\textsuperscript{th} and 8\textsuperscript{th} week.\textsuperscript{7} In contrast, a study by Busse on 289 adult subjects with mild to moderate asthma, 80\% of whom were on concurrent ICS, showed that, when compared to zafirlukast, salmeterol produced significantly greater improvement in A.M. and P.M. PEFR, less diurnal PEFR variability, fewer symptoms, and less \textit{prn} use of short-acting \textit{β}-agonist (SABA).\textsuperscript{5} \textbf{[LEVEL 3]}

Based on these head-on comparative studies, LABA is the preferred drug over anti-LTs in the majority of asthmatics still symptomatic despite use of ICS. Some patients, particularly those with EIB and those in whom inhaler compliance is not assured, may respond better to anti-LTs. Anti-LTs should be considered if patients on both ICS and LABA are still not controlled.

Since anti-leukotrienes appear to modulate leukotriene activity whose production is not decreased by ICS, it naturally poses as a more attractive anti-inflammatory agent than LABA or theophylline. The bronchodilator effects seen with Zileuton, a leukotriene synthesis modifier, were greater than that reported with theophylline effects seen with Zileuton, a leukotriene synthesis modifier. Since anti-leukotrienes appear to modulate leukotriene activity whose production is not decreased by ICS, it naturally poses as a more attractive anti-inflammatory agent than LABA or theophylline. The bronchodilator effects seen with Zileuton, a leukotriene synthesis modifier, were greater than that reported with theophylline effects given on top of ICS.\textsuperscript{3} No other head-on comparison of these two class of compounds as add-on therapy has been done.

References:


Question No. 10: \textit{How safe are the anti-leukotrienes?}

Answer:

Anti-leukotrienes (anti-LTs) are safe drugs even for prolonged use \textbf{[GRADE A].}

Summary of Evidence:

The Antileukotriene Working Group has clearly established the safety of anti-LTs even when given for prolonged periods of time.\textsuperscript{1} \textbf{[LEVEL 1]} An analysis of four 13-week RCTs of similar methodology assessing efficacy and safety of anti-LTs, showed that of the 1484 asthmatics, 560 or 64\% in the zafirlukast group and 391 (65\%) in the placebo group developed adverse effects.\textsuperscript{2} In one of these studies, extended by Grossman to 39 more weeks, the most common adverse events noted were pharyngitis (zafirlukast and placebo 24.2\%) and headache (zafirlukast, 13.0\%; placebo, 10.9\%).\textsuperscript{3,4}

A similar study assessing safety and tolerability of montelukast reported the same frequency of adverse reactions.\textsuperscript{5} \textbf{[LEVEL 1]}

Anti-LTs should be used with caution among patients with liver disease, although more recent studies failed to implicate direct hepatotoxicity with leukotriene receptor antagonist use. Churg-Strauss syndrome, a rare severe eosinophilic granulomatous lung disease, has been reported to be associated with anti-LT use (1:20,000 asthma cases), noted particularly during the period of oral steroid tapering.\textsuperscript{6,7,8,9} It was proposed that this situation may be due to the unmasking, rather than causation of Churg-Strauss syndrome. The syndrome may have mistakenly diagnosed as asthma and initially controlled with oral steroids. Once the oral steroid dose has decreased during tapering, then the syndrome resurfaced.\textsuperscript{8,10-11}

References:


**Question No. 11:**

**What is the recommended dose for anti-leukotrienes in asthma?**

**Answer:**

Below are the recommended initial adult dosages of the available anti-LTs in the Philippine market:

- **Montelukast:** 10 mg (5 - 10 mg) H.S., P.O.
- **Zafirlukast:** 20 mg (range: 20 - 80) b.i.d. (one hour before or two hours after a meal) P.O.

In both preparations, higher dosages have been used, but only modest additional improvements of asthma parameters were seen. The effective dose is continued up to 3 months after which, the anti-LT can be stopped if asthma control is good. **[LEVEL 4]**

**References:**


**Reliever Medications**

**Question No. 1:**

**Are inhaled short-acting β₂-agonists administered regularly safe and effective for maintenance therapy?**

**Answer:**

No, inhaled short-acting β₂-agonists (SABA) administered regularly is neither safe nor effective as maintenance therapy. Regular use of SABA has been shown to increase hyperresponsiveness, significantly decrease asthma control, cause deterioration in the objective measures of pulmonary function, and increase mortality. Therefore, inhaled SABA should only be used on an 'as-needed' basis **[GRADE A]**.

**Summary of Evidence:**

A 26-week, randomized, multi-center, double-blind placebo-controlled trial conducted by the National Institute of Health in patients with mild asthma, compared effects of regularly scheduled salbutamol with as-needed dosing. There were no deleterious nor beneficial effects derived from the regular use of inhaled salbutamol beyond those derived from the use of the drug on as-needed basis. **[LEVEL 1]** Lower values in the evening peak flow and short-term bronchodilator response to inhaled salbutamol were noted in the regularly scheduled group, but these were judged to be not clinically significant. During a withdrawal period in the study, there was no deterioration in lung function observed in either group. In one of the treatment groups, an increase in airway hyperresponsiveness was observed after two weeks of regular therapy. The study concluded that inhaled salbutamol should be prescribed for patients with mild asthma on an 'as-needed' basis.

Similar studies done by Sears and Cockcroft also showed that regular four-times-a-day treatment with SABA is not more beneficial than its use on a prn basis. Although regular use of SABA showed a consistent trend toward more symptoms, reduced lung function and increased airway responsiveness, the differences for all outcomes except airway hyperresponsiveness, did not achieve significant levels. **[LEVEL 1]**

The more potent SABA, like fenoterol, seem to have more adverse effects when taken regularly. Several studies demonstrated clear evidence that regular use of fenoterol was associated with increased morbidity and mortality due to increased severity of asthma. In New Zealand, the use of high-dose fenoterol was associated with a second epidemic of asthma mortality during the late 1970s. Case control studies subsequently confirmed that fenoterol use was a significant predictor of mortality independent of asthma severity. Other studies further demonstrated that the higher risk associated with fenoterol was attributed solely to the use of higher doses, and that regular use of fenoterol resulted in poorer asthma control, compared with as-needed use. The decline in the use of fenoterol in New Zealand in 1990 led to reduction in both asthma mortality and hospitalizations for severe asthma. These findings suggested that the excess mortality was related to severe asthma exacerbated by fenoterol use. A meta-analysis of epidemiological studies concluded that the apparent association between β₂-agonist use and increased mortality applied only to nebulized therapy. **[LEVEL 1]**

**References:**

The safety of ‘as-needed’ formoterol was also evaluated [LEVEL 2] increased the time to first severe exacerbation over [LEVEL 2] Furthermore, as-needed formoterol use significantly [LEVEL 2] rescue medication had 38% fewer severe exacerbations [LEVEL 2] Of the two inhaled LABA available, formoterol has [LEVEL 2] LABA as rescue medication, its role as such should always be with caution. More controlled studies along this line will validate its role.

Other Treatment/Medication

**Question No.1:**

*Can allergen-specific immunotherapy be used in the management of asthma?*

**Answer:**

Yes, numerous studies have shown that allergen specific immunotherapy can be used in the management of asthma [GRADE A].

**Summary of Evidence:**

Several double-blind, placebo-controlled studies have been conducted on the efficacy of specific immunotherapy, using various allergens such as house dust mites, pollens, cat and dog dander. These studies show that specific immunotherapy may result in a significant decrease in asthma medication consumption and improvement in symptom scores and FEV₁.

Likewise, there is decreased skin and bronchial sensitivity to the allergen among patients undergoing immuno-

**Question No.2:**

*Is there a role for long acting β₂-adrenergic agonists as rescue medication?*

**Answer:**

Yes, long-acting β₂-agonists with rapid onset of action may be used as rescue medication [GRADE B].

**Summary of Evidence:**

Of the two inhaled LABA available, formoterol has a more rapid onset of action, and its role as rescue medication has been investigated extensively. Studies have shown that it relieves bronchoconstriction as rapidly as salbutamol¹ and as effectively as terbutaline.²³⁴ [LEVEL 2]

A study by Ind comparing the clinical efficacy and safety of terbutaline and formoterol used as rescue medications¹ showed that both drug were similarly effective. The probability of not having a severe exacerbation was similar for both groups and the difference was not statistically significant. For both groups, the mean number of rescue inhalations used was similar. In another study by Tattersfield et al, patients who used formoterol as rescue medication had 38% fewer severe exacerbations per patient than those who used terbutaline.³ Furthermore, as-needed formoterol use significantly increased the time to first severe exacerbation over a period of 12 weeks compared with terbutaline. [LEVEL 2]

The safety of ‘as-needed’ formoterol was also evaluated and compared to that of terbutaline. These studies show that formoterol, when used as rescue medication, was as safe and well tolerated as terbutaline. No relevant differences were noted between treatments in terms of adverse events, ECG changes, serum potassium concentrations, or other potential systemic side effects. Moreover, no tolerance to the bronchodilating effect was observed.

Another study evaluated the initial effects of treatment with formoterol in children over 12-16 years using an open, randomized, and parallel-group design.² This study likewise showed that, in children, treatment with formoterol was as well tolerated as treatment with terbutaline.

**References:**

therapy. Some of the most significant improvements were seen in the studies involving dust mite allergens. However, many trials involving cat, dog, cockroach and pollens have also shown significant results.\[LEVEL 1\] A meta-analysis of randomized controlled trials on immunotherapy clearly demonstrated symptomatic improvement with immunotherapy (odds ratio of 2.7, 95% CI: 1.7 to 4.4); medication reduction with house dust mite immunotherapy (odds ratio of 4.2, 95% CI: 2.2 to 7.9) and reduction in bronchial hyperreactivity (odds ratio of 13.7, 95% CI 3.8 to 50).\[LEVEL 1\]

References:

Question No. 2:
Is immunotherapy safe?

Answer:
Yes, immunotherapy is a relatively safe treatment modality [GRADE A].

Summary of Evidence:
Most studies did not reveal any significant harmful effects from immunotherapy.\[LEVEL 1\] A meta-analysis done in 1995 revealed systemic reactions in 32% (95% CI) of patients receiving immunotherapy as compared with 18% of patients receiving placebo.\[LEVEL 1\] It is strongly advised that patient selection be strict, and that a specialist perform this procedure in a clinic setting, with emergency drugs on hand. Patients undergoing immunotherapy should be observed for up to two hours after the procedure, as this is the time when the most serious complications (e.g. anaphylaxis) may occur. Patients with unstable or steroid dependent asthma are usually at an increased risk for severe reactions and therefore should be excluded from receiving immunotherapy.

References:

Recommendation
Referral to a specialist for specific allergen immunotherapy should be considered when avoidance measures are not possible and appropriate medication fails to control symptoms of allergic asthma.

Question No. 3:
What is the role of cromones in the management of chronic asthma?

Answer:
Cromones may be used in young asthmatics and in those with atopy, nocturnal and exercise-induced asthma [GRADE A].

Summary of Evidence:
Both cromolyn sodium and nedocromil sodium may be used in the management of asthma particularly in children, in atopic young adults, and in patients with nocturnal asthma and exercise-induced bronchoconstriction. The main hindrances to its efficacy are the frequent daily dosing (up to four-times-a-day) as well as the unpleasant taste.

Several studies have compared the efficacy of cromolyn sodium and nedocromil sodium to placebo, inhaled short-and long-acting \(\beta\)\textsubscript{2}-agonists, inhaled steroids, oral theophylline, and against each other. Most studies comparing these drugs with placebo have revealed statistically significant improvements in all indexes of asthma symptoms including quality of life, pulmonary function measures and bronchodilator use.\[LEVEL 1\] When compared to inhaled SABA, cromolyn sodium and nedocromil sodium showed improved efficacy in patients with atopy.\[LEVEL 2\] Long-acting \(\beta\)\textsubscript{2}-agonist like salmeterol, however, showed greater improvement in most pulmonary parameters when compared to the cromones.\[LEVEL 2\] Studies involving theophylline and cromolyn sodium and nedocromil sodium showed that efficacy of these drugs are comparable as far as improvement in asthma symptoms and lung function are concerned.
References:


Recommendation

The use of cromones should be limited to patients who are unwilling or unable to include inhaled steroids in their asthma regimen.

Question No. 4:

Do antihistamines have a role in the management of chronic asthma?

Answer:

The role of antihistamines is limited to providing relief of allergic symptoms in some asthmatics. [GRADE B]

Summary of Evidence:

Some patients with both atopy and asthma may benefit from antihistamines. Several studies, however, have shown that these drugs may be more useful for allergic rhinitis rather than bronchial asthma as there is no decrease in bronchial responsiveness to methacholine after antihistamine treatment. [LEVEL 2]

Other studies also show that although antihistamines may help inhibit the early asthma response, they have no effect on the late asthma response. [LEVEL 2]

Studies involving the use of ketotifen and terfenadine have shown improvement in symptomatology of allergic asthma compared to placebo, but only after 2-4 weeks of continuous use. [LEVEL 2] These drugs, therefore, are inferior when compared to long acting β₂-agonists and steroids in both the relief and control of asthma symptoms. [LEVEL 2]

References:


Management Strategy for Chronic Asthma

Question No. 1:  
What is the recommended treatment of chronic asthma?

Answer:
The management of chronic stable asthma depends on the level of severity of the condition. [GRADE A]

In the chronic management of persistent asthma, controller medications which have been invariably used are: inhaled corticosteroids, long acting β₂-agonists, leukotriene antagonists, theophylline and oral steroids. Anti-inflammatory therapy, specifically inhaled corticosteroids, has been most effective in achieving asthma control in these patients. In contrast, intermittent asthma is not considered an indication for continuous use of ICS. The mainstay reliever medication, however, remains to be a SABA, which is recommended for use on a prn basis for all levels of severity. Table 5 shows the recommended severity-based therapy for chronic asthma.

The introduction of the fixed single inhaler combination ICS plus LABA represents a major advance in asthma treatment since the first edition of the Philippine Consensus Report on Asthma. These fixed-combination inhalers are effective across the whole spectrum of persistent asthma, from mild to severe persistent disease.1-7 [LEVEL 1] Furthermore, many patients with severe persistent asthma who used to require maintenance oral steroids can be kept under control with the ICS plus LABA single inhaler alone.8,9

With the combination inhaler, a significant proportion of mild to moderate persistent asthmatics can be symptom free with even half the ICS dosages previously required.1,5,10-12 The salutary effects of the combination inhaler are thought to be due to the complementary actions of the component drugs acting on the same site of the airways.13-16 Their availability through more user-friendly gadgets and their twice-a-day dosing have contributed to improving patient compliance. Furthermore, since lower corticosteroid doses were found to be just as effective in combination with a LABA when compared with previously utilized moderate to higher doses, this has somewhat allayed fears of systemic side effects. Also, the reduced daily drug cost of the combination preparations when compared with the two components taken separately is also likely to enhance patient adherence.17-19

The broad efficacy of combination inhalers makes the strategy of micro-staging of asthma severity unnecessary. [LEVEL 4] As such, the severity levels of mild persistent and moderate persistent asthma may be lumped together into one category. This revolutionary approach to managing mild and moderate persistent asthma as a single asthma category has gained relevance in the light of recent findings on the underutilization of ICS noted in the asthma survey results conducted in the Philippines. A sub-analysis of the data on the Asthma Insights and Reality in Asia-Pacific (AIRIAP) study clearly indicates the low usage of ICS is the reason why a big proportion of Filipino asthmatic patients continue to suffer from persistent symptoms.20 A device, which delivers both ICS plus LABA, therefore, is bound to be more acceptable for a greater majority of these patients, especially since ICS itself does not produce the immediate relief experienced with bronchodilators. Better compliance and fewer defaults are, therefore, expected. Continued use of anti-inflammatory medications correlates with better asthma control. With the array of doses available for the combination inhalers, their early use in mild persistent asthma patients is not at all disadvantageous and greatly simplifies the management approach. For the more severe persistent cases, the combination ICS plus LABA in a single inhaler would also be just as effective. However since the functional airway compromise may be more marked in these patients, significant improvement in symptomatology and lung function may take effect only after a few days. Prudence, therefore dictates that these patients be given a course of oral steroids at the start of treatment in moderate to high doses which can then be subsequently tapered to a level that would maintain the asthma under control.

References:
8. Aubier M et al. Salmeterol/fluticasone propionate (50/500 µg) combination in a discus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. Respir Med 1999;93:876-84.
50/100 µg bid) is more effective than budesonide (400 µg bid) in mild to moderate asthma (abstract no. p. 162) Eur Respir J. 1998; 12 Suppl 29:20s.


Chapter 7
Patient Education

Question No. 1:
Does patient education have a role in asthma management?

Answer:
Yes, patient education is considered by many national and international consensus guidelines as a key and essential component of successful asthma management.

[GRADE A]

Summary of Evidence:
Asthma, although a chronic condition, is also a highly variable and episodic condition. Current management approaches require asthmatics and their families to effectively carry out complex and multiple pharmacologic regimes. Asthmatics, therefore, should possess the basic knowledge and understanding of the mechanisms of action of the different drug prescriptions, the mastery of inhaler techniques, and the ability to adhere to prolonged and maintained drug therapy, even during asymptomatic periods. In addition, the asthmatic and his or her caregiver must have the capability to recognize early warning signs of an acute (especially severe) exacerbation, make rapid decisions about symptom severity, institute rational self-medication, and determine when to seek medical advice. Finally, that he or she must be prepared to make lifestyle changes and institute environmental control strategies.

Patient education is thought to be the mechanism through which patients can learn to successfully accomplish these tasks. Education is considered to be necessary "to help patients gain the motivation, skills and confidence to control their asthma."1,2,3 [LEVEL 1]

References:


Question No. 2:
Does asthma patient education improve health care outcomes?

Answer:
Yes, well-designed asthma patient education programs reduce the frequency of asthma morbidity indices over a wide range of patient populations. [LEVEL 1]

Formal asthma education programs, aside from improving symptom control, can likewise enhance self-care behavior. [LEVEL 2].

Summary of Evidence:
A systematic review of 22 randomized controlled trials recently compared the effects of asthma self-management education programs coupled with regular practitioner review with the usual care in adult patients.1 Self-management education was found to significantly reduce hospitalizations, emergency room visits, unscheduled visits to the doctor, days off work or school, and nocturnal asthma. However, measures of lung function were not significantly changed. [LEVEL 1] Interventions for educating children who have attended the emergency room for an asthma exacerbation have found similar improvement in disease outcomes.2 [LEVEL 1] A recent review by the Education and Delivery of Care Working Group at the first World Asthma Meeting reinforced these findings.3

A local study conducted at the Philippine General Hospital compared adult asthmatics enrolled at an existing asthma self-management program and an enriched
education program with a control group who received usual care. The study showed that at three months post-intervention, patients who were enrolled in either formal education programs showed significant improvement in different facets of asthma self-efficacy, including level of confidence in performing self-care behavior, decision-making, communication, knowledge of preventive medication and symptom management. Compared with the control group, these patients also demonstrated significant change toward correct inhaler technique.

References:

Question No. 3: Which educational strategies and methods have been found to be effective in influencing clinical outcomes?

Answer:
Educational strategies that focus on individuals or small groups employing multiple interactive educational methods, and incorporating self-management skills transfer, self-monitoring modalities, and regular practitioner review have been found to be effective. However, strategies that are limited to the transfer of information about asthma, its causes and its treatment have not been shown to improve health outcomes [GRADE A].

Summary of Evidence:
A recent review showed that published asthma educational programs for adults vary widely in terms of general and educational objectives, teaching techniques, tools, content, assigned trainers, duration of intervention and number of sessions. Thus, this precludes replication and reduces the possibility of identifying the most effective components. Nevertheless, a systematic review of 11 randomized controlled trials of variable quality showed that limited asthma education (information only) among patients aged 16 years and above did not reduce hospitalization for asthma and had no effect on doctor visits, lung function and medication use. The effects of these education programs on asthma symptoms were variable. There was no reduction in days lost from normal activity. [LEVEL 1] Moreover, programs relying primarily on providing books or videotapes to asthma patients were successful only in improving knowledge. [LEVEL 1]

Very few studies have addressed the optimal method for educational intervention. As described in the previous section, programs that focus on asthma self-management skills and are coupled with regular practitioner review, rather than usual care, improve morbidity indices. Sub-analyses of these clinical trials showed that those that involved individualized written asthma action plans showed greater reduction in hospitalization than those that did not. [LEVEL 1]

Asthma education should ideally begin in the physician’s office and this can be effective only in the presence of

| Table 6.1 Treatment based on Asthma Severity* |
|----------------|----------------|
| **Severity** | **Recommended Treatment** |
| | **Daily controller medications** | **Alternative controller** | **Reliever medications** |
| Intermittent | None needed | ICS high dose or ICS regular dose plus any of the ff: SR theophylline, Antileukotriene, Oral SR β₂-agonist | SABA as needed |
| Mild to Moderate Persistent | ICS + LABA combination as single inhaler | | SABA as needed |
| Severe Persistent | Oral steroids + ICS + LABA combination as single inhaler + any of the ff: SR theophylline, Antileukotriene, Oral SR β₂-agonist | | SABA as needed |

* Available in the Philippines
appropriate asthma therapy.\(^6\) [LEVEL 3] With regards to the comparison between educational programs focused on individuals versus those using small groups, there appeared to be few differences in outcomes, although small-group teaching resulted in a slight decrease in frequency of exacerbations, possibly because of the influence of peer support.\(^5,7\) [LEVEL 2]

As to the issue of PEF self-monitoring, this practice may be useful in some patients, particularly those who are poor perceivers of airflow obstruction. Patient self-monitoring may be effective using either measurement of PEF or monitoring of symptoms.\(^8,9,10\) [LEVEL 1]

**References:**


**Recommendation**

Patient education is a key and essential component of successful asthma management. Education is a necessary tool not only as means to acquire knowledge about the condition but also to help patients gain the motivation, skills and confidence to control their asthma.

Well-designed asthma education programs have been shown to be effective in reducing asthma morbidity indices over a wide range of patient population.

**Chapter 8**

**Special Considerations**

**Exercise-Induced Asthma (EIA)**

**Question no. 1:**

*What is the mechanism of exercise-induced asthma (EIA)?*

**Answer:**

The heat exchange theory is currently one of the top theories for bronchoconstriction associated with exercise (EIA).\(^1,2,3,4,5,6,7\) [LEVEL 2]

During exercise, the humidification and heating function of the nose is bypassed and cold air reaches the airways, which in turn produces bronchial spasm. This theory also suggests that the cold air may produce a humoral effect or a nerve reaction in the small airways that leads to bronchospasm.\(^8\) Neurohumoral transmitters like leukotrienes have also been implicated in mediating a portion of the airway narrowing.\(^9,10\)

Leukotrienes have been found to play a role in airway refractoriness with repeated bouts of exercise. They may act through release of inhibitory prostaglandins or by inhibiting other mediator release. [LEVEL 3]

**References:**


**Question No. 2:**

*How is exercise-induced asthma controlled?*
Answer:
Exercise-induced asthma may be controlled through non-pharmacological or pharmacological means. [GRADE B]

Summary of Evidence:
Non-pharmacologic treatment entails avoiding inclement atmospheres and choosing a sport that is less likely to induce an asthmatic attack. A third strategy would be by inducing the known refractory period a few times earlier in the day of competition so that at the time of exercise competition, the neurohumoral transmitters are exhausted.1

Pharmacological treatment methods can be divided into primary and secondary methods. The primary pharmacological agents given by inhalation are the β₂-agonists, which will prevent exercise-induced bronchospasm in more than 80% of asthmatics. The most common are the rapid-acting, short-duration β₂-agonists like salbutamol and terbutaline.2,3 The next most common are the rapid-onset, long duration formoterol and the slower-onset, long-duration β₂-agonist salmeterol.4,5,6 [LEVEL 2]

Secondary of adjunctive treatment would be the use of agents for long-term control of asthma like inhaled corticosteroids8 cromolyn8 and antileukotrienes.9 [LEVEL 3] The role of theophylline and anticholinergic agents are not clearly defined.

References:

Food Allergy

Question No. 1:
Is there an association between food allergy and asthma exacerbations?

Answer:
Yes, the association between food allergy and asthma has now been clearly established. [GRADE B]

Summary of Evidence:
There is evidence that respiratory responses, including bronchoconstriction and increased airway hyperresponsiveness, have been demonstrated in individuals following positive food challenges.1 However, food-induced asthma in adults is actually not very common, with an incidence of only 2-8.5%.2,3 The clinical correlation of food allergy with asthma is much higher in children at 17%.4 [LEVEL 2]

Multiple food allergy is generally uncommon. In infants and children, the majority of allergic reactions are due to milk, eggs, soy, peanuts and wheat5-6, while in adults, the most common food allergens are peanuts, tree nuts, fish, shellfish, and eggs.7-8 [LEVEL 2]

Sulfite-containing foods have been shown to cause bronchospasm and severe asthmatic attacks in sensitive asthmatic patients, although the mechanism by which sulfate agents worsen asthma is unknown.9-12 The relationship between monosodium glutamate (MSG) and asthma is more controversial with several groups reporting both association and non-association.13-17 [LEVEL 3] The mechanism by which MSG produces asthma attacks is not well understood. There is conflicting evidence as to whether MSG exacerbates or induces asthma or if it alters airway reactivity. Tartrazine (FD & C Yellow No. 5) and other dyes commonly used for artificial coloring of food, drink, pills and tablets have been reported to cause urticaria and asthmatic symptoms in a few sensitive patients.18-19 [LEVEL 3]

Asthma exacerbated by food allergy should be suspected in the following circumstances:
- If asthma started early in life, especially if associated with atopic dermatitis
- If asthma associated with a current or past history of food allergies or atopic dermatitis
- If wheezing after specific foods has been noted
- If asthma poorly controlled even with appropriate medications and aeroallergen avoidance.

Food-induced asthma may present acutely, occurring within minutes to one hour of food ingestion, manifesting initially with itchy watery eyes and nose, and itchiness in the mouth. This may later on progress to deep, repetitive coughing, shortness of breath, and wheezing. Acute attacks of asthma may be severe and occasionally progress to systemic anaphylaxis and even death. Respiratory reactions from food allergens may also be subtle, at times presenting only with cough, chronic asthma, or increased BHR.20

The diagnosis of food allergy is dependent on adequate history and physical examination, skin testing or in vitro antigen-specific IgE tests, results of an appropriated exclusion diet and blinded provocation when this may
be performed safely.

Food-induced asthma is confirmed if food challenge reveals wheezing, a significant drop in FEV₁, or a positive methacholine challenge on the test day but not on the placebo day. Elimination of the suspected food is often tried as part of a diagnostic approach. If symptoms resolve, confirmation by food challenge is recommended, except in cases wherein the patient has a convincing history of systemic anaphylaxis to a specific food.

Following identification of allergenic food, strict elimination of that food is the only treatment proven effective to prevent reactions. The use of oral desensitization, prophylactic medications, or immunotherapy has not yet been demonstrated in well-designed studies to have clear efficacy in the management of food allergies. [LEVEL 2]

References:

Asthma and Gastroesophageal Reflux Disease

Question No. 1:
What is the relationship between asthma and gastroesophageal reflux disease (GERD)?

Answer:
Like asthma and sinusitis, GERD and asthma frequently coexist, but there have been no convincing evidence confirming the role of GERD in triggering or aggravating asthma. [GRADE C]

Summary of Evidence:
A relationship between GERD and asthma was first documented in the late 1960s when asthma patients were reported to be "cured" of asthma following surgery for hiatal hernia and/or GERD. Additional research has continued to show that reflux may cause or trigger asthma symptoms. [LEVEL 3]

There were two accepted mechanisms for the role of GERD in asthma. The first hypothesis states that the stimulation of esophageal mucosal receptors produces vagally mediated bronchospasm. Prolonged reflux clearance time often causes symptomatic esophageal disease and esophagitis, consequently increasing the sensitivity of esophageal receptors to refluxed material. Once stimulated, the receptors transmit a signal that results in constriction of the bronchioles. The second hypothesis is the micro- or macro-aspiration of gastric contents into the lungs, especially in the supine position of sleep, causing a chemical pneumonitis. More recent research, however, has suggested that although aspiration does occur on rare occasions, it is unlikely to be the primary reason for reflux-triggered asthma.

More recently, a third mechanism being proposed is heightened bronchial reactivity secondary to esophageal reflux. In one study of 105 consecutive asthmatics, the degree of methacholine reactivity correlated with the number of episodes of reflux during 24-hour esophageal pH monitoring. [LEVEL 3] Furthermore, nocturnal esophageal acid events are associated with lower respiratory resistance.
Asthma and the Menstrual Cycle

Question No. 1: Does menstrual cycle affect the course of asthma?

Answer:
No direct correlation exist between the airway hyperresponsiveness in asthma and hormonal changes in the menstrual cycle [GRADE C]

Summary of Evidence:
Premenstrual asthma (PMA) is a phenomenon first described by Frank in 1931, as a symptom of "premenstrual tension." Large-scale longitudinal studies have not yet been undertaken to adequately address just how prevalent the condition is. Several small studies, however, seem to suggest that 30-40% of female asthmatics experience a premenstrual worsening of symptoms but these were retrospective and based on patient-recorded recollections of subjective data without any objective finding of increased asthma severity. Modest reductions in peak flow rate at the time of menstruation for affected women compared to unaffected women were noted, but these were not usually associated with clinical deterioration.

Two small prospective uncontrolled studies on the influence of menstrual cycle on airway responsiveness reported no significant difference on FEV1, or medication use before or after the menstrual period. Asthma control, however, deteriorated just prior to and during menses. A small prospective cohort study by Pauli et al in 1989 showed significant worsening of asthma symptoms, slight decline of peak expiratory flow rates but no deterioration in spirometric values showing airway responsiveness among asthmatics during menses. A larger prospective analysis of data from 182 nonpregnant asthmatic women presenting to the emergency room for acute asthma reported that nearly half of all exacerbations occurred during the period from two days before until four days after the onset of menses.

The weight of evidence seems to suggest that there is at least a subset of female patients with asthma who develop morbidity in conjunction with their menstrual cycle. A study by Shames showed that this distinct subset of women are the older asthmatics with more severe disease and longer duration of symptoms.

References:
1. Frank RT. The hormonal causes of premenstrual tension. Arch Neurol. Psych. 1931;26;1053.

Question No. 2: Why does worsening of asthma occur in these patients during menstruation?

Answer:
The precise cause of worsening of asthma during menstruation is thought to be related to changing levels of progesterone or prostaglandins. Current studies, however, presently do not show any definite correlation between airway responsiveness and the absolute levels of these substances [GRADE C].

Summary of Evidence:
Progestrone levels fall in the days before menstruation and it has a relaxant effect on airway smooth muscle contractility. Thus, this may lead to cyclic changes in airway responsiveness in women prone to perimenstrual exacerbation of asthma. Progesterone-induced hyperventilation may further influence asthma leading to symptomatic deterioration and dyspnea. Although an increase in asthma symptoms and a decrease in peak expiratory flow rates have been demonstrated in the luteal phase of the menstrual cycle, there seems to be no deterioration in airway reactivity. It must be emphasized, however, that there is no real relationship between airway function and absolute levels of progesterone.

Prostaglandins have previously been reported to have

References:

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bronchoconstrictive effects; endogenous prostaglandin synthesis, however, has not been shown to correlate with occurrence of premenstrual asthma.\(^4\)

The lack of definitive evidence for either progesterone or prostaglandin mediation has led to several other theories that are under investigation.\(^5\) These theories are as follows:

- "Allergy" to endogenous hormones
- Psychological changes associated with the premenstrual syndrome
- Progesterone potentiation of an unidentified bronchodilator
- Progesterone-mediated loss of microvascular integrity with subsequent edema leak
- Dynamic fluctuations of estrogen levels after sustained but static elevation
- Increase in mucus secretions that may accompany menstruation

Further clarification of and investigation into these mechanisms need to be undertaken to provide more information and insight into the pathogenesis of the effect of asthma on the menstrual cycle or vice versa.

References:


Question No. 3:

**Does treatment of premenstrual asthma differ from the usual treatment of asthma exacerbations?**

Answer:

No, the treatment options include the usual medications for asthma. Intramuscular progesterone, however, may be effective in women with severe, refractory premenstrual asthma. [GRADE C]

Summary of Evidence:

Treatment of perimenstrual asthma entails the usual asthma medications, namely: β\(_2\)-agonists, anticholinergics, and corticosteroids. Intramuscular progesterone was shown to be more effective in women with severe, refractory premenstrual asthma, eliminating the decrease in peak flow rate, as well as reducing total corticosteroid requirement.\(^6\) [LEVEL 4]

The use of danazol, intramuscular medroxyprogesterone acetate or gonadotropin-releasing hormone agonists to suppress menstrual cyclicity remains a promising area of investigation.

Reference:


**Occupational Asthma**

**Question No. 1:**

**Is occupational asthma a common condition?**

Answer:

Although occupational asthma is the most common occupational lung disease in developed countries,\(^1\) very few prevalence data has been published for many developing countries including the Philippines.

Occupational exposures have been estimated to cause 5-15% of adult-onset asthma.\(^5\)\(^6\)\(^7\) The prevalence of occupational asthma due to agents with high molecular weight is generally less than 5% while prevalence due to low molecular weight agents is 5-10%.\(^7\)

References:


**Question No. 2:**

**When should you suspect occupational asthma?**

Answer:

An occupational cause should be considered for all new cases of asthma in adults.\(^1\) [GRADE D]

A detailed occupational history of past and current exposure to possible causal agents in the workplace, work processes and specific job duties should be obtained. A history of asthma beginning during a working lifetime should lead to consideration of occupational asthma. The classic history is one of a worker whose asthma is worse at work, with improvement during weekends or holidays. However, this pattern may often be absent because symptoms are also usually present outside the workplace, being triggered by exposure to irritants, such
as cold air, fumes or exercise.

Questionnaires, although sensitive and essential in the assessment, are not specific tools. In a study on workers suspected to have occupational asthma, the predictive value of a positive questionnaire was 63% and a negative questionnaire was better at 83%. Another study showed that clinical history has a high sensitivity of 96% but a low specificity of 25% for the diagnosis of occupational asthma.2 [LEVEL 4]

References:

Question No. 3:
What is the approach to the patient suspected of having occupational asthma?

Answer:
As opposed to other occupational lung diseases like pneumoconiosis in which the diagnosis is based only on exposure history and chest x-ray abnormalities, occupational asthma needs to be confirmed by objective means.1 [GRADE D]

The first step following history and physical examination is to confirm objectively that the patient has asthma. Spirometry before and after bronchodilator therapy should be assessed within 24 hours of typical workplace exposure or at a time when symptoms are present. If spirometry is normal, then bronchoprovocation using either methacholine or histamine should be performed to determine the presence or absence of airways hyperresponsiveness. A normal methacholine response in a symptomatic patient who is still working, rules out occupational asthma.

Once the diagnosis of asthma is objectively confirmed by pulmonary function tests, the next step is to assess objectively the relationship of asthma to work. This could be done by challenge testing with the specific suspected agent or by serial monitoring of PEF for a period at work and a similar period away from work.2,3 Sensitivity and specificity of PEF monitoring in confirming occupational asthma are 81% and 74%, respectively.4 Combining PEF monitoring with serial assessments of bronchial responsiveness using histamine or methacholine can provide further objective evidence.5 When the above results are inconclusive, serial spirometry performed throughout the work shift is advisable.

Early referral and rapid access to a specialist and a specialized center where investigations can be arranged is needed because the diagnosis is often difficult to establish in those who have left work and cannot or will not return. [GRADE A]

References:

Question No. 4:
How should patients with occupational asthma be managed?

Answer:
The ideal treatment is the permanent removal of patients with occupational asthma from exposure to the causal agent. [GRADE A]

During the period of diagnostic investigations and following diagnosis, the patient should have appropriate treatment for asthma, consistent with recent asthma guidelines.

Unfortunately, studies indicate that the majority of patients with occupational asthma are left with some degree of permanent lung function impairment.1 Over 60% of subjects fail to recover even after removal from exposure. The best prognosis is seen among those with early diagnosis, early removal from further exposure to the sensitizer, and in those with milder asthma at the time of diagnosis.2,3

The patient with occupational asthma should be considered to represent a 'sentinel event' in the workplace. Consideration should be given to the possibility of occupational asthma in other exposure workers, and appropriate measures should be taken to reduce the risk of further exposure to the offending agent. [GRADE A]

References:
Asthma and Pregnancy

Question No. 1: 
*Does the course of asthma change during pregnancy?*

Answer:
Asthma may remain unchanged, become worse, or improve during pregnancy. [LEVEL 2]

**Summary of Evidence:**
Approximately 4% of pregnancies are complicated by bronchial asthma. The true prevalence may be even higher; at least 10% of the population appears to have nonspecific airway hyperreactivity, a hallmark of asthma.\(^1\) The course of asthma during pregnancy is variable; it may remain unchanged, become worse or improve during pregnancy. In a prospective study by Steinus-Aarniala et al, 42% of pregnant asthmatics required more medications, 40% were managed with the same medications before pregnancy and 18% actually needed less medications.\(^2\) [LEVEL 1]

As a rule, women with more severe asthma prior to pregnancy are likely to deteriorate during pregnancy. The factors most likely contributing to worsening asthma during pregnancy include upper respiratory tract infections and patient non-compliance with medical regimens.\(^3\) [LEVEL 2] The peak of exacerbations appears between the 24\(^{th}\)-36\(^{th}\) weeks of gestation (AOG). Asthma generally remains quiescent during labor and delivery in about 90% of pregnant women. Whatever the course of asthma may be during pregnancy, changes generally revert to pre-pregnancy level of severity within 3 months post-partum.\(^4\)

**References:**

Question No. 2: 
*How does maternal asthma affect pregnancy outcome?*

Answer:
When asthma is properly controlled, pregnant women with asthma can maintain a normal pregnancy with little or no increased risk to themselves or their fetuses. [GRADE B]

**Summary of Evidence:**
Uncontrolled asthma during pregnancy has been proven to produce serious maternal and fetal complications. Both mother and child are at risk if asthma is not well managed during pregnancy. Severe persistent asthma has been related to the development of maternal complications like pre-eclampsia, maternal hypertension, hyperemesis gravidarum, uterine vaginal hemorrhage, toxemia, placenta previa, and induced complicated labors.\(^1\) Severe asthma requiring emergency therapy or corticosteroid seem to be associated with an increased incidence of perinatal complications like pre-eclampsia, low-birth weight infants, perinatal mortality, preterm births and hyperbilirubinemia. However, these associations did not reach statistical significance.\(^4\)

**References:**

Question No. 3: 
*Are asthma medications safe to use during pregnancy?*

Answer:
Most asthma medications are safe to use during pregnancy. [GRADE B]

**Summary of Evidence:**
The use of inhaled \(\beta_2\)-agonist, theophylline, cromolyn, antihistaminics and inhaled steroids are not associated with major congenital malformations when used at anytime during gestation, including the first trimester.\(^1\) [LEVEL 3] In a review of ten studies on asthmatic women during the first trimester of pregnancy, only three met the relevant quality criteria.\(^1\) There was no significant increase in the rate of congenital malforma-
tion with any of the exposures.6 [LEVEL 2]
Because few safety studies on medication use during pregnancy are available, the US Food and Drug Administration (FDA) has published pregnancy risk categories for drugs. (See Table 6) All commonly used asthma medications fall under safety categories B and C. This system was developed from animal exposure data and epidemiologic data from population studies.5

For mild intermittent asthma and acute exacerbations in all asthmatic patients, inhaled short-acting β2-agonists is the preferred treatment. These agents have not been shown to have any adverse effects on pregnancy outcomes or teratogenic effects on the fetus.1 Use of oral and parenteral β2-agonists should be avoided because of lack of safety data, the increased risk of side effects (e.g. tremor), and the potential to inhibit delivery.

Inhaled corticosteroids are the 'gold standard' for controlling all forms of persistent asthma. [LEVEL 1] These agents have been shown to decrease asthma exacerbations and mortality and improve overall quality of life. The 2000 position paper of the American College of Obstetricians and Gynecologist and the American College of Allergy, Asthma and Immunology states, "it would not be unreasonable to continue a different inhaled corticosteroid in a patient well-controlled by that drug prior to pregnancy."6

Long-acting β2-agonists, salmeterol and formoterol are the preferred adjunctive therapy to inhaled corticosteroids for managing moderate to severe persistent asthma. [LEVEL 1] Although no adequate or well-controlled human data are available on salmeterol and formoterol use during pregnancy, there are also no reports of congenital defects. Use of an inhaled long-acting β2-agonist with an inhaled corticosteroid appears to be acceptable during pregnancy, especially if the patient has taken such agents without problems before the pregnancy.7

Long-term safety data are available for inhaled cromolyn and it is a feasible option for use during pregnancy especially if there is a concern about prescribing inhaled corticosteroids.8 The leukotriene receptor antagonists, zafirlukast and montelukast sodium are classified as FDA category B because no human or animal teratogenic effects have been seen with agents. Use of oral corticosteroids during pregnancy poses some risk.9

Theophylline has not been shown to have teratogenic effects during pregnancy although its use has radically decreased because of possible toxicity with elevated serum levels and because of the development of newer, safer agents. When used during pregnancy, clearance of the agent decreases, therefore dosing should be carefully watched and adjusted. Theophylline crosses the placenta and the newborn may have jitterness, increased heart rate and even vomiting at birth.9

Nebulized ipratropium can be used for acute asthma not responding well to inhaled β2-agonist. Ipratropium bromide is an inhaled anticholinergic agent that is used as an adjunctive therapy to short-acting β2-agonists for acute asthma exacerbations. Animal data have not demonstrated any birth defects, but human data are lacking.10

Omalizumab, an IgG monoclonal antibody directed against IgE, was recently approved in the United States for use in moderate to severe allergic asthma that has not responded to moderate to high doses of inhaled corticosteroids. The FDA gave this agent a pregnancy category B rating because no teratogenic effects were seen in animal studies. In clinical studies with omalizumab before FDA approval, several women became pregnant and delivered normal infants. Because of the newness of this agent, caution should be exercised when prescribing during pregnancy.11

References:

Question No. 4: Are steroids associated with increased risk of perinatal complications?

Answer: Inhaled corticosteroids have no effect on pregnancy outcome and do not increase the risk to the fetus. [GRADE B] However, the use of oral steroids for severe asthma during pregnancy may be associated with increased perinatal complications.
Summary of Evidence:
Review of literature on human studies do not show any evidence of teratogenicity with the use of inhaled corticosteroids during pregnancy. The most published information is on beclomethasone, and it does not appear to have any adverse effect on pregnancy outcome and does not increase the risk to the fetus. Likewise, a study with more than 2000 patients did not show an increased rate of congenital malformations with the use of inhaled budesonide. Among 293,948 births identified from 1995 to 1998 derived from the Swedish Medical Birth register, pregnancy outcomes were compared for mothers reporting asthma medication usage with those for women who reported no usage. Researchers found that 2,968 mothers who reported use of inhaled budesonide during early pregnancy gave birth to infants of normal gestational age, birth weight, and length; there was no increase in rate of stillbirths or multiple births. Because of this data, budesonide has been assigned a safety category B rating by the FDA. At present, all other inhaled corticosteroids are category C.

On the other hand, oral steroids have been associated with risk for pre-eclampsia in several studies. Whether or not this link represents a drug effect or is a marker of severity cannot be ascertained. The use of oral steroids during the first trimester has also been associated with oral cleft palate deformities and prednisone treatment throughout the pregnancy is associated with lower birth weights. The benefit of using oral steroids, when indicated however, far outweighs the risk of uncontrolled asthma to the mother and fetus.

References:

Asthma and Surgery

Question No. 1:
*Are patients with asthma undergoing surgery at greater risk for peri-operative complications?*

Answer:
No, the risk of peri-operative complications in patients with asthma undergoing surgery is low. [GRADE B]

Summary of Evidence:
Generally, the risk of peri-operative complications in patients with asthma undergoing surgery is low. [LEVEL 2] Warner et al reviewed the records of 706 diagnosed asthmatics who had at least one surgical procedure involving a general anesthetic or central neuroaxis block. The frequency of perioperative bronchospasm and laryngospasm was low in his cohort of patients with asthma. The frequency of complications was increased in older patients and in those with active asthma. The frequency of complications did not depend on the severity of asthma symptoms or the chronic use of bronchodilators before operation.

A computer-aided study of 136,929 patients by Olsson in 1987 found the incidence of intraoperative bronchospasm to be 0.80% in 3,210 patients with asthma versus 0.16% in those patients without asthma. Bronchospasm during anesthesia occurred in only one out of 634 anesthetics or 1.7 per 1000 patients. This author concluded that there was the likelihood of increased incidence of intraoperative complications (bronchospasm) in the presence of pre-existing airway obstruction, particularly in the face of airway instrumentation. [LEVEL 4]

References:

Question No. 2:
*Are steroid-controlled asthmatics at risk for developing peri-operative complications?*

Answer:
No, there is no increased risk for peri-operative complications in steroid-controlled asthma. [GRADE B]

Summary of Evidence:
The use of pre-operative steroids to control asthma does not put the asthmatic at greater risk for peri-operative complications. [LEVEL 2] Prior to surgery, patients...
Asthma and Upper Airway Disease

Question No. 1: Is there a relationship between asthma and rhinitis established?

Answer: No, there is no established relationship between asthma and rhinitis, however, they commonly occur as co-morbidities. [GRADE B]

Summary of Evidence: The concept of "one airway, one disease" was proposed in the late 1990s because of several common factors noted between asthma and rhinitis: common epidemiologic, pathologic, and physiologic characteristics and a common therapeutic approach.2,3

A study which utilized a standard questionnaire in 478 patients demonstrated that rhinitis is nearly a universal phenomenon in patients with allergic asthma, occurring in 99% of adults and 93% of adolescents.6 [LEVEL 4] Conversely, asthma has also been shown to affect up to 38% of patients with allergic rhinitis which is substantially higher than the 3-5% prevalence noted in the general population.7 Even nonallergic rhinitis was also found to be associated with asthma.8,9,10 [LEVEL 3]

Allergic rhinitis often precedes or occurs at the same time as asthma. However, although atopic subjects commonly have coexisting asthma and rhinitis, rhinitis alone does appear to be a risk factor for asthma.11 Settipane et al noted that in a 23-year follow up study of 690 college freshmen without asthma, those who reported nasal symptoms in 1961 developed asthma three times more often (10.5%) than individuals without rhinitis (3.6%).12-13 [LEVEL 3]

Although it appears that patients with rhinitis are more likely to develop asthma, it has not been possible to predict which patients are at greatest risk. Patients with allergic rhinitis and no clinical evidence of asthma have been shown to frequently exhibit bronchial hyperresponsiveness to methacholine. This has given rise to the postulate that BHR may represent an intermediate phase between

Reference:

Table 6. US FDA Pregnancy Risk Categories for Asthma Medications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>C</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>C</td>
</tr>
<tr>
<td>Triamcinolone acetate</td>
<td>C</td>
</tr>
<tr>
<td>Fluticasone/salmeterol</td>
<td>C</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>B</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>B</td>
</tr>
</tbody>
</table>

Risk Categories:
A - Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.
B - Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women or Animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
C - Animal studies have shown adverse effects on the fetus, but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks; or there are no animal reproduction studies and no adequate studies in humans.
D - There is no evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X - Studies in animals or humans demonstrate fetal abnormalities, or adverse reaction reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefits.
nential rhinitis and asthma: is it the same disease? Allergy 1997;52:20-8.

Question No. 2: Is there a relationship between asthma and sinusitis?

Answer: Yes, it appears that asthma and sinusitis frequently co-exist, and sinusitis can trigger asthma. However, as shown in some studies, their causal relationship remains controversial. [GRADE B]

Summary of Evidence:
Whether the relation between asthma and sinusitis is causal or merely an epiphenomenon of an infectious or immune-mediated disease affecting the entire respiratory tract is still a matter of debate. However, there are certain characteristics that identify those patients in whom sinusitis may play an important role in the pathogenesis of asthma. These are as follows:

- Sinusitis preceding the development of asthma symptoms
- Sinusitis in non-atopic patients (which implies that a fundamental change has occurred in the sinus tissues and airway)
- Aspirin sensitivity
- Corticosteroid dependency (suggests that an underlying sinus disease may be a trigger for asthma)
- Patients with asthma who are refractory to appropriate treatment
- When a child with asthma becomes symptomatic while taking medications that were formerly effective
- When a patient receives a short-term course of steroid therapy for an acute episode of asthma and is still symptomatic after several days of treatment

Approximately 40-60% of asthmatic patients will show radiographic evidence of sinusitis. Some patients with recurrent sinusitis will develop chronic tissue inflammation with mucosal thickening and formation of nasal polyps, also called chronic hyperplastic sinusitis and nasal polyp formation (CHS/NP). Pathologic examination of this tissue typically shows a striking inflammatory infiltrate of eosinophils, somewhat similar to the inflammatory infiltrate seen in asthma. In patients with coexisting asthma, the development of CHS/NP often heralds a worsening in asthma symptoms.

It was also postulated that a sino-nasal bronchial reflex exists which could be mediated by the autonomic nervous system or inflammatory mediators such as leukotrienes, prostaglandin D, and histamine. Other possible explanations include micro- or macro-aspiration of sinus drainage, or a systemic effect of cytokines. These hypotheses have all raised the issue of whether sinusitis can contribute to the development of asthma and whether sinusitis and asthma share a common pathogenetic mechanism.

Although etiology may be murky, there are several empirical studies, which suggest that treatment of sinusitis or rhinitis may improve asthma symptoms. For example,
in a study of 48 children with sinusitis and asthma, a reported improvement in asthma symptoms was generally noted after medical treatment for sinusitis.\(^3\) \([\text{LEVEL 4}]\) In another series of studies, Slavin and colleagues reported on the effect of sphenoethmoidectomy in a series of adult patients with difficult to control asthma and medically resistant sinusitis.\(^1\) A total of 65% of patients reported significant improvement in their asthma symptoms after the procedure.

References:

Vaccines and Asthma

Question No. 1: \textit{Does influenza vaccination have a role in asthma management?}

Answer:
Yes. Influenza vaccination has been found to decrease the incidence of asthma exacerbations.\(^{1,3}\) \([\text{GRADE A}]\)

Summary of Evidence:
Immunization with influenza vaccine is safe and not associated with any significant side effects in adult patients with persistent asthma. Although pulmonary function abnormalities may occur as a complication of vaccination, the risk of pulmonary complications is very small and outweighed by the benefits of vaccination.\(^1\) \([\text{LEVEL 1}]\) There are no data from the published literature on whether pneumococcal vaccines lead to asthma exacerbation.

International guidelines recommend the immunization of patients with chronic pulmonary disease, including asthma, against influenza and pneumococcus. Despite these recommendations, many asthmatic patients do not receive vaccination because of some reports that vaccination, particularly influenza, may lead to asthma exacerbation. A double-blind placebo-controlled multi-centre crossover study was undertaken to assess the safety of influenza vaccine in patients with asthma.\(^2\) Among 225 participants with paired data, PEF fell to greater than 20% of baseline in 11 patients given the vaccine compared to three patients on placebo, and PEF fell more than 30% in eight patients given the vaccine compared with none after placebo. However, when participants with colds were excluded from the analysis, no significant difference was noted in the number of patients whose PEF fell more than 20% between vaccine and placebo. It was also noted that there was a significant difference in patients whose PEF decreased more than 30% from baseline between the vaccine and the placebo group. These findings indicate that pulmonary function abnormalities may occur as a complication of influenza vaccination, however, the risk of pulmonary complications is very small. \([\text{LEVEL 2}]\)

In a double-blind study by Steinus-Aarmiala et al in 1988, 318 adult patients with chronic asthma were randomly allocated to receive either active vaccine or placebo.\(^3\) Follow-up for eight months after the vaccination revealed no difference in asthmatic symptoms between the patients treated with active vaccine and those receiving placebo. \([\text{LEVEL 2}]\)

References:

\textbf{Appendix A}

\textbf{Abbreviations}

\begin{tabular}{|l|l|}
\hline
\textbf{AHR/BHR} & Airway/Bronchial Hyperresponsiveness \\
\textbf{Anti-LTs} & Anti-leukotrienes \\
\textbf{AOG} & Age of Gestation \\
\textbf{BAL} & Bronchoalveolar Lavage \\
\textbf{BDP} & Beclomethasone Dipropionate \\
\textbf{BMD} & Bone Mineral Density \\
\textbf{BUD} & Budesonide \\
\textbf{CS} & Corticosteroid \\
\textbf{CHS/NP} & Chronic Hyperplastic Sinusitis and Nasal Polyp \\
\textbf{DPI} & Dry Powder Inhaler \\
\textbf{EBV} & Epstein-Barr Virus \\
\textbf{ECHRS} & European Community Health Survey \\
\textbf{ED} & Emergency Department \\
\textbf{EIA} & Exercise Induced Asthma \\
\textbf{EIB} & Exercise Induced Bronchoconstriction \\
\textbf{ETS} & Environmental Tobacco Smoke \\
\textbf{FACET} & Formoterol and Corticosteroids Establishing Therapy \\
\textbf{FEV\textsubscript{1}} & Forced Expiratory Volume in 1 second \\
\textbf{FP} & Fluticasone Propionate \\
\textbf{FVC} & Forced Vital Capacity \\
\textbf{GERD} & Gastro Esophageal Reflux Disease \\
\textbf{GINA} & Global Initiative for Asthma \\
\textbf{GRASSIC} & Grampian Asthma Study of Integrated Care Trial \\
\textbf{HEPA} & High Efficiency Particulate Air Cleaner \\
\textbf{HFA} & Hydrofluorokane \\
\textbf{HPA} & Hypothalamus-Pituitary-Adrenal \\
\textbf{ISAAAC} & International Study of Asthma and Allergy in Childhood \\
\textbf{ICS} & Inhaled Corticosteroid \\
\textbf{IgE} & Immunoglobulin-E \\
\textbf{IL-4} & Interleukin 4 \\
\textbf{IL-5} & Interleukin 5 \\
\hline
\end{tabular}
Appendix B

Summary of Criteria for Rating Evidence

Table I. Levels of Evidence for Rating Studies on the Accuracy of Diagnostic Tests

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>All 5 of the following criteria are satisfied:</td>
</tr>
<tr>
<td></td>
<td>a. There was an independent interpretation of the results of the diagnostic test (without knowledge of the results of the gold standard).</td>
</tr>
<tr>
<td></td>
<td>b. There was an independent interpretation of the results of the gold standard (without knowledge of the results of the diagnostic test).</td>
</tr>
<tr>
<td></td>
<td>c. The study of patients consisted patients (but not known) to have the disorder of interest.</td>
</tr>
<tr>
<td></td>
<td>d. The diagnostic test and gold standard are both described in sufficient detail to allow reproducibility.</td>
</tr>
<tr>
<td></td>
<td>e. The study population consists of at least 50 patients with and 50 patients without the disorder of interest.</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>4 of the 5 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>3 of the 5 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>2 of the 5 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 5</strong></td>
<td>1 of the 5 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 6</strong></td>
<td>None of the 5 criteria are met.</td>
</tr>
</tbody>
</table>

Table II. Levels of Evidence for Rating Studies on the Effectiveness of Treatment

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>A randomized controlled trial (RCT) that demonstrates a statistically significant difference in at least one major outcome - e.g., survival or major illness OR if the difference is not statistically significant, a RCT of adequate size to exclude 25% difference in relative risk with 80% power given the observed results.</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>A RCT that does not meet the level 1 criteria.</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>A non-randomized trial with concurrent controls selected by some systematic method (i.e., not selected on the basis of perceived suitability for one of the treatment options).</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>Before-after study or case series (at least 10 patients) with historical controls or controls drawn from other studies.</td>
</tr>
<tr>
<td><strong>Level 5</strong></td>
<td>Case series (at least 10 patients) without controls</td>
</tr>
<tr>
<td><strong>Level 6</strong></td>
<td>Case series (fewer than 10 patients) or case reports</td>
</tr>
</tbody>
</table>

Table III. Levels of Evidence for Rating Review Articles

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>All of the following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>a. Comprehensive search for evidence</td>
</tr>
<tr>
<td></td>
<td>b. Avoidance of bias in the selection of articles</td>
</tr>
<tr>
<td></td>
<td>c. Assessment of the validity of each cited article; Conclusion supported by the data and analysis presented</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>3 of the 4 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>2 of the 4 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>1 of the 4 criteria are met.</td>
</tr>
<tr>
<td><strong>Level 5</strong></td>
<td>None of the 4 criteria are met.</td>
</tr>
</tbody>
</table>

Table IV. Grading System for Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Grade A</strong></td>
<td>The recommendation is based on one or more studies at Level 1.</td>
</tr>
<tr>
<td><strong>Grade B</strong></td>
<td>The best evidence available is at Level 2.</td>
</tr>
<tr>
<td><strong>Grade C</strong></td>
<td>The best evidence is at Level 3.</td>
</tr>
<tr>
<td><strong>Grade D</strong></td>
<td>The best evidence available is lower than 3, and include experts' opinions, clinical experience, and common sense. These recommendations address practical issues of implementation and other factors existing in the local setting.</td>
</tr>
</tbody>
</table>

### Warnings
- **Do not** use any unrecorded names or codes.
- **Do not** make any assumptions beyond the provided information.
- **Do not** create any new sections or subsections.
- **Do not** alter the table structure or presentation.
- **Do not** modify the content in any way.
- **Do not** add any external references or links.

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**Abbreviations:**
- IL-8: Interleukin 8
- IL-12: Interleukin 12
- IL-13: Interleukin 13
- IFN-γ: Interferon gamma
- LABA: Long Acting β₂-Antagonist
- LT: Leukotriene
- LTRA: Leukotriene Receptor Antagonist
- MDI: Metered-dose Inhaler
- MSG: Monosodium Glutamate
- NO₂: Nitrogen Dioxide
- NEB: Nebulization
- O₃: Ozone
- PCRADM: Philippine Consensus on Asthma Diagnosis and Management
- PC₂₀: Provocative Concentration of Methacholine resulting in a 20% fall in FEV₁ from the baseline
- PEF: Peak Expiratory Flow
- PFT: Pulmonary Function Test
- PM: Particulate Matter
- PMA: Pre-Menstrual Asthma
- PPD: Purified Protein Derivative
- RCT: Randomized Control Trial
- RSV: Respiratory Syncitial Virus
- SABA: Short Acting β₂-Agonist
- SO₂: Sulfur Dioxide
- SR: Slow-release
- TB: Tuberculosis
- TH1: T-helper subtype 1 lymphocyte
- TH2: T-helper subtype 2 lymphocyte
- WHO: World Health Organization
- IL-8: Interleukin 8
- IL-12: Interleukin 12
- IL-13: Interleukin 13
- IFN-γ: Interferon gamma
- LABA: Long Acting β₂-Antagonist
- LT: Leukotriene
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Drugs Mentioned in the Treatment Guideline

This index lists drugs/drug classifications mentioned in the treatment guideline. Prescribing information of these drugs can be found in PPD reference systems.

<table>
<thead>
<tr>
<th>Anticholinergics</th>
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<tbody>
<tr>
<td><strong>Ipratropium Br</strong></td>
<td>Atrovent</td>
</tr>
<tr>
<td><strong>Ipratropium Br/Fenoterol</strong></td>
<td>Berodual</td>
</tr>
<tr>
<td><strong>Ipratropium Br/Salbutamol</strong></td>
<td>Combitvent, Duvent</td>
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<tr>
<td><strong>Tiotropium</strong></td>
<td>Spiriva</td>
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<table>
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<td><strong>Beclomethasone Dipropionate</strong></td>
<td>Qvar</td>
</tr>
<tr>
<td><strong>Budesonide</strong></td>
<td>Asmavent, Budecort, Pharmachemie Budesonide, Cyclocaps</td>
</tr>
<tr>
<td><strong>Budesonide/Formoterol</strong></td>
<td>Symbicort Turbuhaler</td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td>Flixotide, Flixotide Nebule</td>
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<thead>
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<th>Ketotifens</th>
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<td>Quomyl</td>
<td>Zadec/Zadec SRO</td>
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<td>Zaditen</td>
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<td><strong>Montelukast</strong></td>
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<td><strong>Zafirlukast</strong></td>
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<td><strong>Clenbuterol</strong></td>
<td>Spiropent</td>
</tr>
<tr>
<td><strong>Formoterol</strong></td>
<td>Atock, Foradil, Oxis Turbuhaler</td>
</tr>
<tr>
<td><strong>Orciprenaline/Bromhexine</strong></td>
<td>Bisolpent</td>
</tr>
<tr>
<td><strong>Proctacervol</strong></td>
<td>Meptin</td>
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<tr>
<td><strong>Salbutamol</strong></td>
<td>Activent</td>
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<tr>
<td><strong>Airhexal</strong></td>
<td>Syrup</td>
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<tr>
<td><strong>Airomir</strong></td>
<td>Pulmoxyl</td>
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<td><strong>Am-Europharma Salbutamol</strong></td>
<td>Pulmoxcell</td>
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<td><strong>Asbunyl</strong></td>
<td>Ritemed Terbutaline</td>
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<td><strong>Asfrenon</strong></td>
<td>Terbulin</td>
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<td><strong>Asmacaire</strong></td>
<td>Terbusol</td>
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<tr>
<td><strong>Asmafort</strong></td>
<td>Terbutaline/Guaifenesin</td>
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<td>Bricanyl Expectorant</td>
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<td><strong>Asmalin Metered Dose Inhaler</strong></td>
<td>Drugmaker's Biotech</td>
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<td><strong>Asmalin Pulmoneb</strong></td>
<td>Guaifenesin/Terbutaline</td>
</tr>
<tr>
<td><strong>Asvent</strong></td>
<td></td>
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<tr>
<td><strong>Cletal</strong></td>
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<tr>
<td><strong>Drugmaker's Biotech Salbutamol</strong></td>
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<td><strong>Emplusal</strong></td>
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</tr>
<tr>
<td><strong>Hivent</strong></td>
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<tr>
<td><strong>Librentin/Librentin Bronchoneb/Librentin inhaler (CFC free)</strong></td>
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<td><strong>Pharex Salbutamol</strong></td>
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<td><strong>Venticin</strong></td>
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<tr>
<td><strong>Salbutamol/Guaifenesin</strong></td>
<td>Asbunyl Plus</td>
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<td><strong>Asfrenon GF Expectorant</strong></td>
<td>Broncaire Expectorant Syrup</td>
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<td><strong>Drugmaker's Biotech Guaifenesin/Salbutamol Expectorant Venzadril</strong></td>
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<td><strong>Salmeterol xinafoate</strong></td>
<td>Serevent</td>
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<td><strong>Salmeterol xinafoate/Fluticasone</strong></td>
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<td><strong>Terbutaline</strong></td>
<td>Alloxygen</td>
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<td><strong>Doxofylline</strong></td>
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</tr>
<tr>
<td><strong>Theophylline</strong></td>
<td>Asmasoloun, Bronidil (Reformulated)</td>
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<td></td>
<td>Nuelin, Phenedrine</td>
</tr>
<tr>
<td></td>
<td>Theodur, Uni-Dur</td>
</tr>
<tr>
<td><strong>Theophylline/Guaifenesin</strong></td>
<td>Hallex</td>
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<table>
<thead>
<tr>
<th>Other Drugs for Asthma/ COPD</th>
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<tbody>
<tr>
<td><strong>Lagundi</strong></td>
<td>Ascof</td>
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<tr>
<td><strong>Corticosteroids</strong></td>
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<tr>
<td><strong>Betamethasone</strong></td>
<td>Betneton</td>
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<tr>
<td><strong>Chlorphenamine maleate</strong></td>
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<td><strong>Betamethasone/ Dexamethasone maleate</strong></td>
<td>Celestamine</td>
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<td><strong>Prednisolone</strong></td>
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<td><strong>Chlorphenamine maleate Histacort Tablet</strong></td>
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<table>
<thead>
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<tbody>
<tr>
<td><strong>Betamethasone</strong></td>
<td>Betnelan</td>
</tr>
<tr>
<td><strong>Celestone</strong></td>
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<td><strong>Diprosan</strong></td>
<td>Diprosan Tablet</td>
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<td><strong>Drugmaker's Biotech</strong></td>
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<td><strong>Betamethasone</strong></td>
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</table>

<table>
<thead>
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<th>Adrenocorticosteroid hormones</th>
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</thead>
<tbody>
<tr>
<td><strong>Betamethasone</strong></td>
<td>Betnelan</td>
</tr>
<tr>
<td><strong>Celestone</strong></td>
<td>Celestone</td>
</tr>
<tr>
<td><strong>Diprosan</strong></td>
<td>Diprosan</td>
</tr>
<tr>
<td><strong>Drugmaker's Biotech</strong></td>
<td>Drugmaker's Biotech</td>
</tr>
<tr>
<td><strong>Betamethasone</strong></td>
<td>Dexamethasone</td>
</tr>
</tbody>
</table>

| Betamethasone | Decloine |
| Drenex | Oradexon |
| **Oradexon Forte** |  |
| **Dexamethasone Na Phosphate** | Scancortin 5 |
| **Hydrocortisone Na Succinate** | Hydroson organon  
Phoenix Hydrocortisone sodium succinate  
Solu-Cortef  
**Methylprednisolone** | Medrol  
**Methylprednisolone acetate** | Depo-Medrol  
**Methylprednisolone Na succinate** | Adrena  
Solu-Medrol  
**Prednisolone** | Drugmaker's Biotech Prednisolone  
Liquipred  
Optipred  
Ritemed Prednisolone  
**Prednisone** | Drazone  
Drugmaker's Biotech Prednisone  
GXI Prednisone  
Orasone 5/Orasone 20  
Pred 5/Pred10/Pred 20/Pred30/  
Pred 50  
Prednisone Organon  
Prolix  
**Triamcinolone** | Kenacort  
**Triamcinolone acetonide** | Kenacort-A intra-articular/ intradermal |