Asthma

Asthma Description

Asthma is
a disease that affects the lungs
defined as a chronic inflammatory disorder of the airways.

Symptoms of asthma

- In susceptible individuals, this inflammation causes recurrent episodes of:
  - Wheezing
  - Breathlessness
  - Chest tightness
  - Night time or early morning coughing

If someone has asthma, he or she has it all the time, but asthma attacks will occur only when something bothers the lungs.

We know that if someone in the family of a person with asthma has asthma, other family members are more likely to have it too.

In most cases, we don’t know what causes asthma; however, it can be controlled.

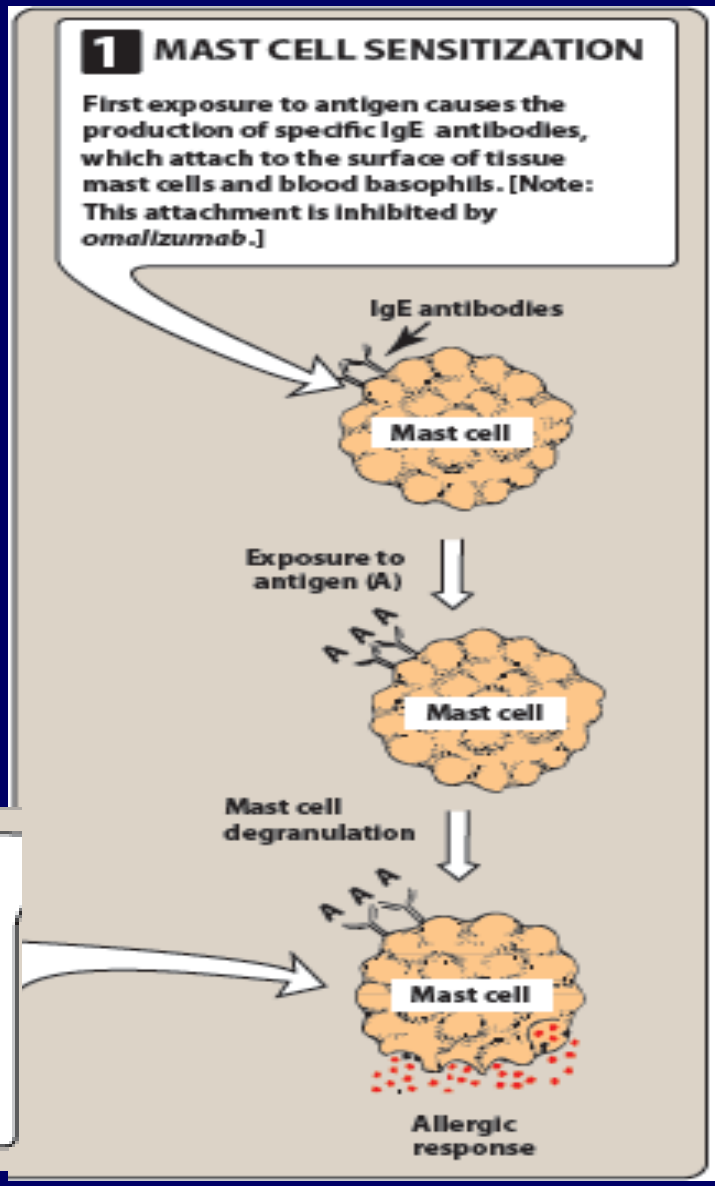
Asthma can be controlled by:
knowing signs of an attack,
staying away from things that trigger an attack
following the advice from a healthcare provider.

Diagnosing Asthma: Spirometry

Test lung function when diagnosing asthma

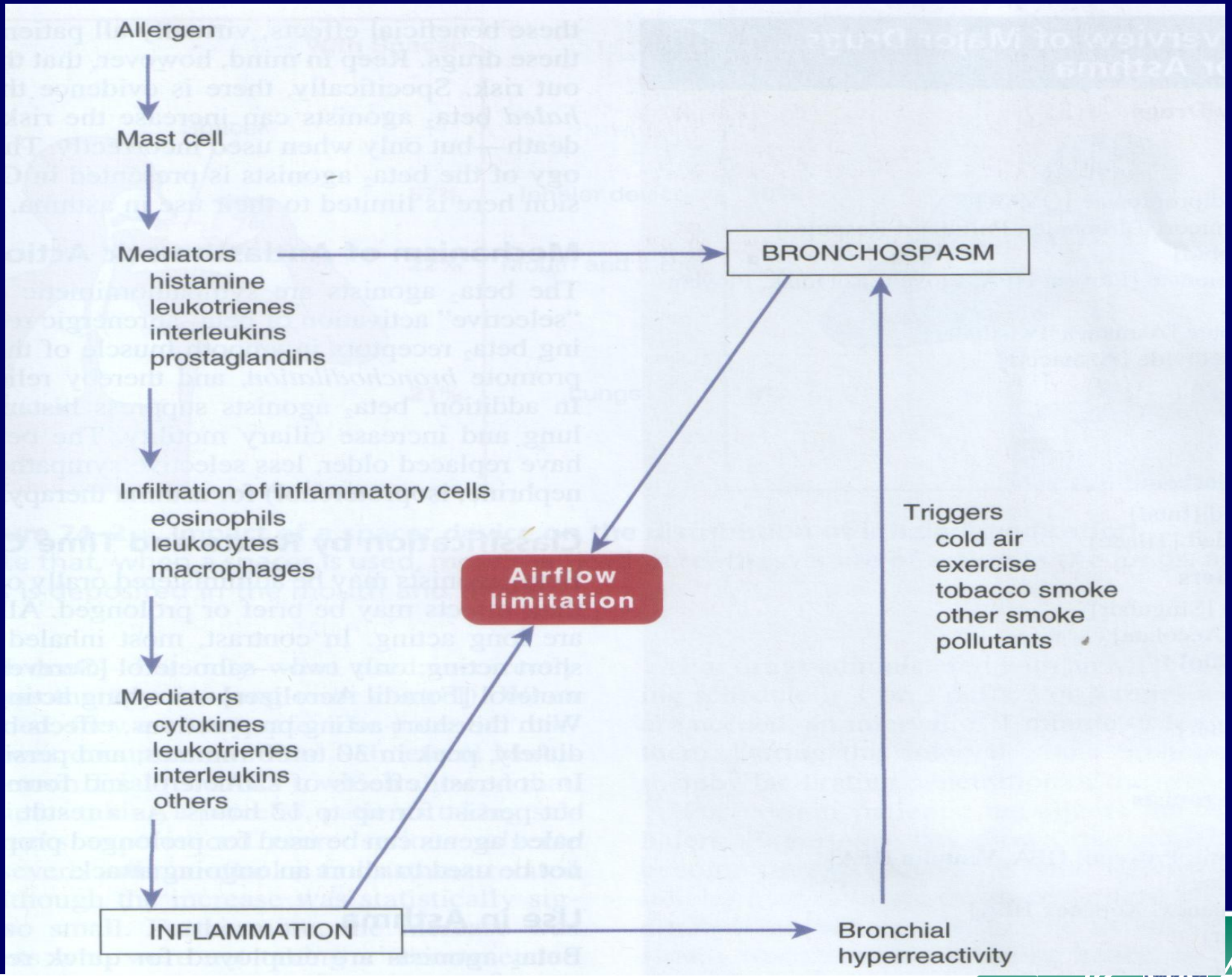
Table 23.1 Examples of asthma trigger factors that may cause asthma

Trigger	Examples
Allergens	Pollens, moulds, house dust mite, animals (dander, saliva and urine)
Industrial chemicals	Manufacture of, for example isocyanate-containing paints, epoxy resins, aluminium, hair sprays, penicillins and cimetidine
Drugs	Aspirin, ibuprofen and other prostaglandin synthetase inhibitors, beta-adrenoceptor blockers
Foods	A rare cause but examples include nuts, fish, seafood, dairy products, food colouring, especially tartrazine, benzoic acid and sodium metabisulphite
Other industrial triggers	Wood or grain dust, colophony in solder, cotton dust, grain weevils and mites; also environmental pollutants such as cigarette such as cigarette smoke and sulphur dioxide
Miscellaneous	Cold air, exercise, hyperventilation, viral respiratory tract infections, emotion or stress



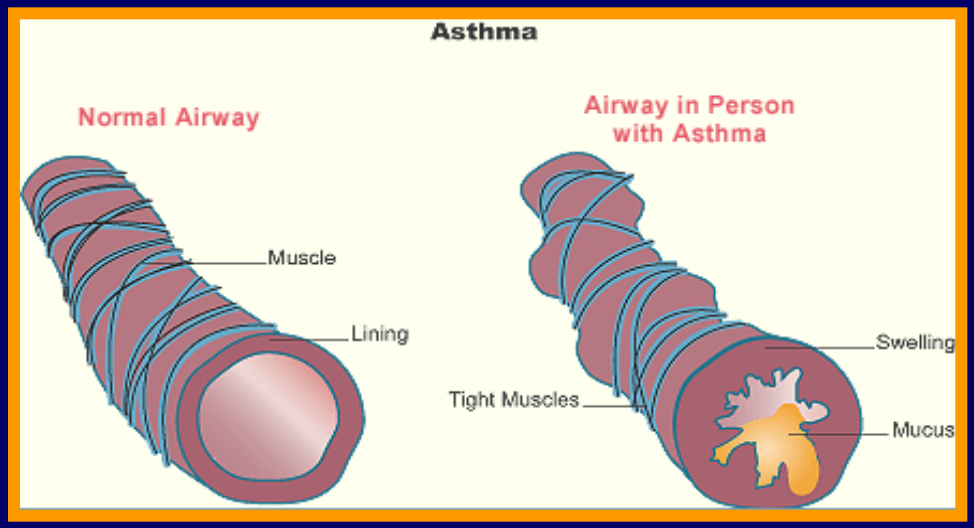
2 MAST CELL DEGRANULATION

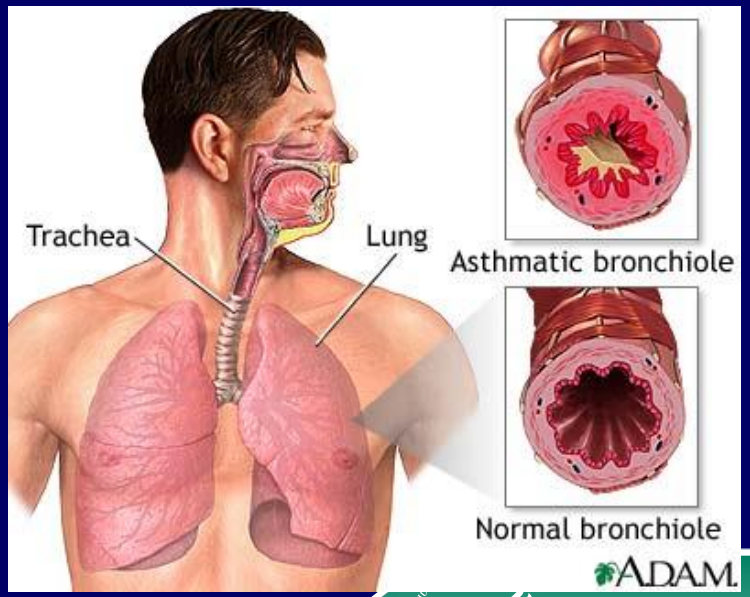
Subsequent exposure to antigen results in binding to surface-bound IgE molecules. The sensitized mast cells are stimulated to release granules containing histamine, leukotrienes, prostaglandins, and other potent chemical mediators.


Allergen
Mast cell
Mediators
histamine
leukotrienes
interleukins
prostaglandins
BRONCHOSPASM
Infiltration of inflammatory cells
eosinophils
leukocytes
macrophages
Airflow limitation
Triggers
cold air
exercise
tobacco smoke
other smoke
pollutants
Mediators
cytokines
leukotrienes
interleukins
others
INFLAMMATION
Bronchial hyperreactivity

Specific Pathophysiology

- With exposure to a trigger, a cascade of cellular responses result in:
  - Increased mucus production
  - Mucosal swelling
  - Bronchial muscle contraction





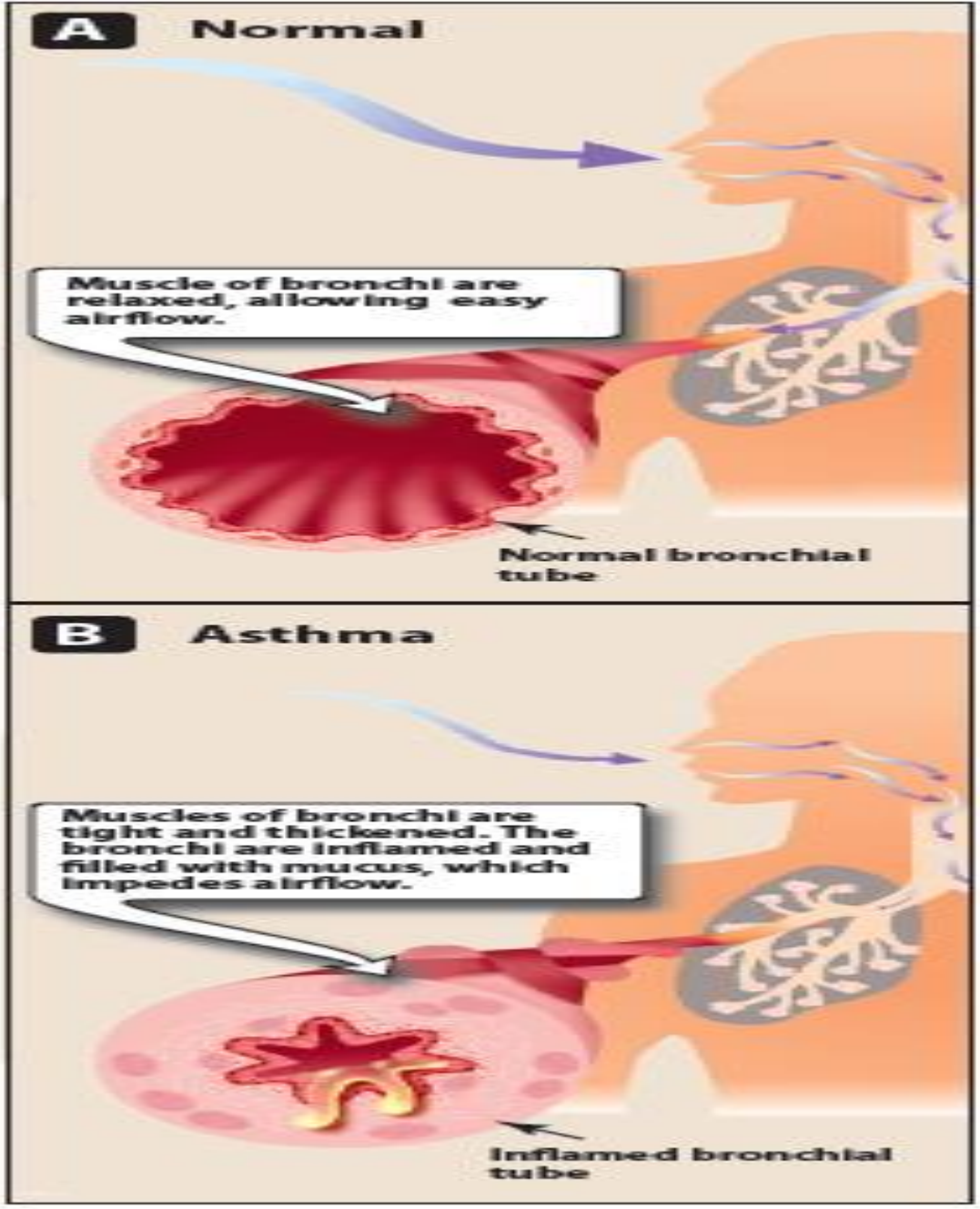


Figure 27.2
Comparison of bronchi of normal and asthmatic individuals.

Can asthma be cured?

- **Asthma can be controlled (but not cured) by:**
  - **Avoiding triggers or reducing exposure to triggers**
  - **Using medication to control symptoms**

TABLE 74–1 • Overview of Major Drugs for Asthma

Anti-Inflammatory Drugs

Glucocorticoids

Inhaled

- Beclomethasone dipropionate [QVAR]
- Budesonide [Pulmicort Turbohaler, Pulmicort Respules]
- Flunisolide [Aerobid]
- Flucticasone propionate [Flovent HFA, Flovent Rotadisk, Flovent Diskus]
- Mometasone furoate [Asmanex Twisthaler]
- Triamcinolone acetonide [Azmacort]

Oral

- Prednisone
- Prednisolone

Cromolyn and Nedocromil

- Cromolyn, inhaled [Intal]
- Nedocromil, inhaled [Tilade]

Leukotriene Modifiers

- Montelukast, oral [Singulair]
- Zafirlukast, oral [Accolate]
- Zileuton, oral [Zyflo]

IgE Antagonist

- Omalizumab [Xolair]

Bronchodilators

Beta$_2$-Adrenergic Agonists

Inhaled: Short Acting

- Albuterol [Proventil, Proventil HFA, Ventolin HFA]
- Bitolterol [Tornalate]
- Levalbuterol [Xopenex, Xopenex HFA]
- Pirbuterol [Maxair]

Inhaled: Long Acting

- Formoterol [Foradil Aerolizer]
- Salmeterol [Serevent Diskus]

Oral

- Albuterol [Proventil, Volmax]
- Terbutaline [Brethine]

Methylxanthines

- Theophylline, oral [Theolair-SR, Theo-24, Uniphyl, others]

Anticholinergics

- Ipratropium, inhaled [Atrovent HFA]
- Tiotropium, inhaled [Spiriva]

Asthma Medications

Bronchodilators

- Sympathomimetics
- Anticholinergics
- Methylxanthene Derivatives

Anti-inflamatory drugs

- Corticosteroids
- Biologic Response Modifiers (Monoclonal Antibodies)
- Leukotriene Receptor Antagonists
- Mast Cell Stabilizers

Medications to Treat Asthma

- **Two major categories of medications are:**
  - Long-term control
  - Quick relief

Medications to Treat Asthma: Long-Term Control

- **are Taken daily over a long period of time**

- **are Used**
  - ✓ **to prevent excess production of mucus,**
  - ✓ **to reduce inflammation and contraction of airway muscles,**
  - ✓ **to improve symptoms and lung function**
    - Inhaled corticosteroids
    - Long-acting beta$_2$-agonists
    - Leukotriene modifiers

Medications to Treat Asthma: Quick-Relief in acute episodes

- Generally short-acting beta$_2$agonists
- **Used** to relax muscles around the airways to improve breathing

Bronchodilators (Sympathomimetics)

Inhaler

- Albuterol (salbutamol) (short-acting)
- Salmeterol (long-acting)
- Formoterol (long-acting)

Oral

- Albuterol
- Terbutaline

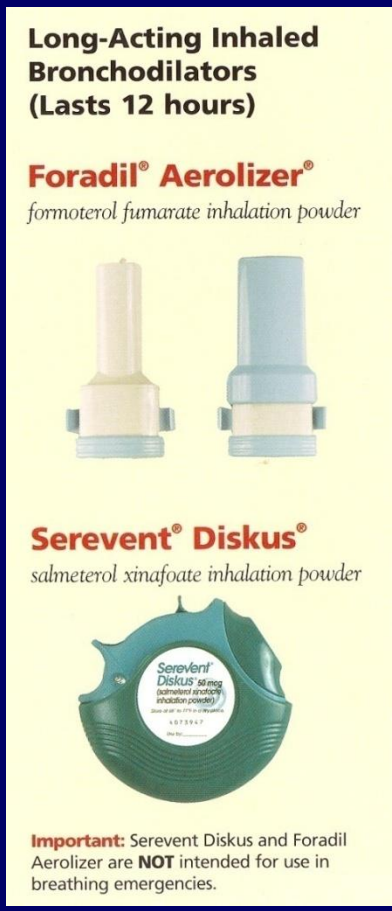


TABLE 74–2 • Beta$_2$-Adrenergic Agonists Used in Asthma

Drug [Trade Name]	Formulation	Initial Dosage	
		Adults	Children
Inhaled Agents: Short Acting			
Albuterol			
[Proventil, Proventil HFA, Ventolin HFA]	MDI (90 mcg/puff)	2 puffs every 4–6 hr PRN	2 puffs every 4–6
[Proventil, AccuNeb]	Solution for nebulization	2.5 mg every 4–6 hr PRN	0.63–2.5 mg/kg ev
Bitolterol mesylate			
[Tornalate]	Solution for nebulization	1.5–3.5 mg 2–4 times/day PRN	1.5 mg 2–4 times/
Levalbuterol			
[Xopenex HFA]	MDI (45 mcg/puff)	2 puffs every 4–6 hr PRN	2 puffs every 4–6
[Xopenex]	Solution for nebulization	0.63 mg every 6–8 hr PRN	0.63 mg every 6–8
Pirbuterol			
[Maxair]	MDI (200 mcg/puff)	2 puffs every 4–6 hr PRN	2 puffs every 4–6
[Maxair Autohaler]	BA-MDI (200 mcg/puff)	2 puffs every 4–6 hr PRN	2 puffs every 4–6
Inhaled Agents: Long Acting			
Formoterol			
[Foradil Aerolizer]	DPI (12 mcg/puff)	1 puff every 12 hr	1 inhalation every
Salmeterol			
[Serevent Diskus]	DPI (50 mcg/inhalation)	1 inhalation every 12 hr	1 inhalation every
Oral Agents			
Albuterol			
[Proventil]	Tablets, syrup	2 or 4 mg 3–4 times/day	2 mg 3–4 times/da
[Proventil Repetabs, Volmax]	Tablets (extended release)	8 mg every 12 hr	4 mg every 12 hr
Terbutaline			
[Brethine]	Tablets	5 mg 3 times/day	2.5 mg 3 times/day

BA-MDI = breath-activated metered-dose inhaler, DPI = dry-powder inhaler, HFA = hydrofluoroalkane propellant, MDI = metere

$Beta_2$ adrenergic agonists

✓ given by inhalation, the most effective drugs for relieving acute bronchospasm and preventing exercise-induced bronchospasm.

✓ by activating $Beta_2$ receptors in smooth muscle of the lung, they result in *bronchodilatation.*

✓ Long-term formulations (orally or by inhalation) are used for long-term control of asthma.

WARNING !!! They are not first-choice agents. They should not be used alone because of increased risk of severe asthma and asthma-related death.

✓ tachycardia, angina and tremor are systemic side effects of these drugs happening rare

Bronchodilators (Anticholinergics)

- ❖ Ipratropium, Tiotropium
- ✓ are muscarinic antagonists
- ✓ are administrated by inhalation
- ✓ are long-acting agents

Most common advers reactions are:

Dry mouth and irritation of pharynx

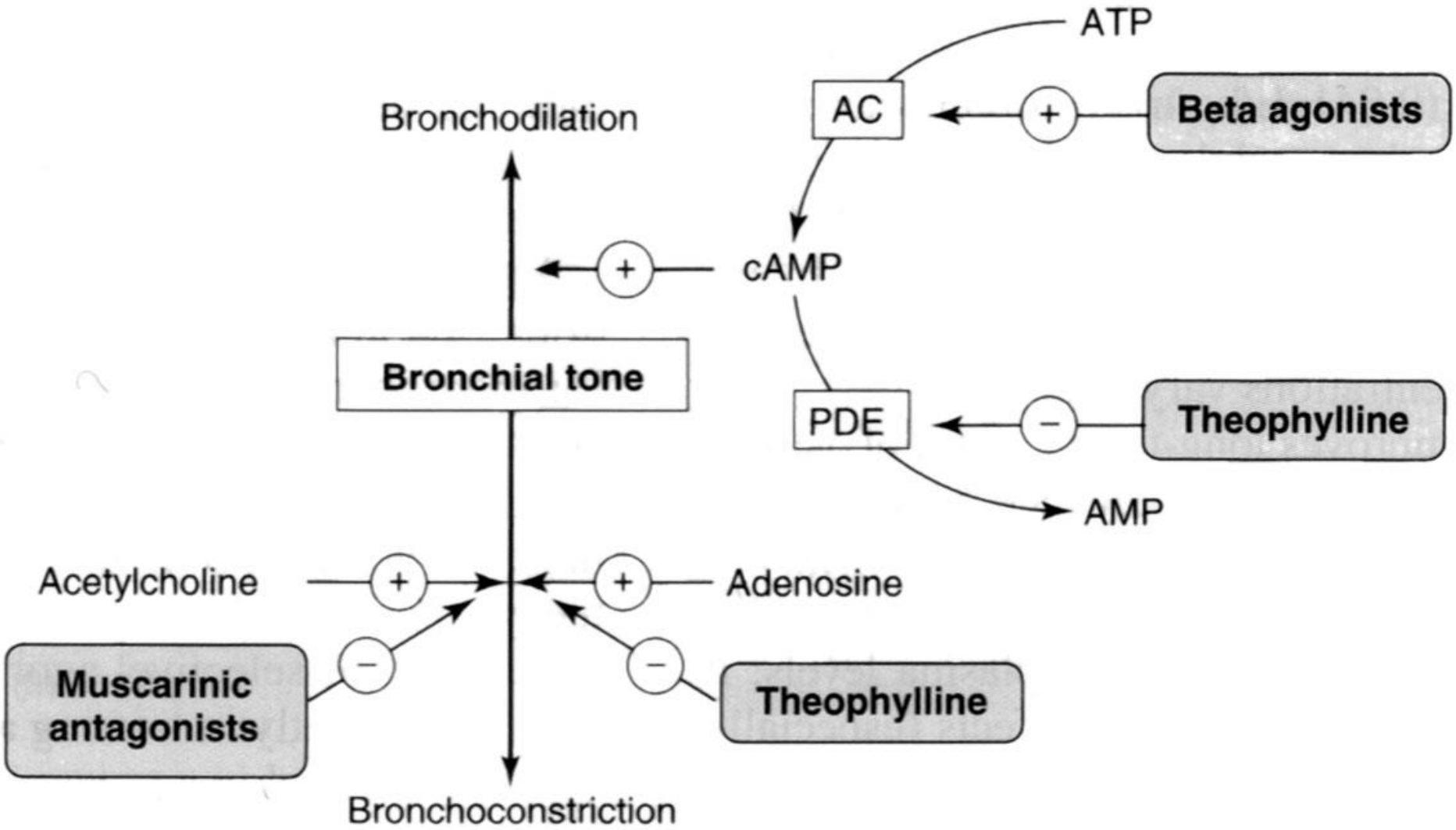
Methylxanthene Derivatives

- Theophylline

used orally

for long-term control

less effective than beta$_2$ agonists


ATP
AC
+
Beta agonists
Bronchodilation
cAMP
+
Bronchial tone
PDE
−
Theophylline
AMP
Acetylcholine
+
+
Adenosine
Muscarinic antagonists
−
−
Theophylline
Bronchoconstriction

Inhaled Corticosteroids

- **Beclamethasone**
- **Budesonide**
- **Flunisolide**
- **Triamcinalone**

- ✓ Are First-line therapy for asthma
- ✓ should be daily used in patients with moderete to severe asthma
- ✓ are very safe
- ✓ The most common side effects are *oropharyngeal candidiasis and dysphonia*
- ✓ *To minimize , gargle after each administration and employ a spacer device. If candidiasis developes, can be treated with antifungal drug.*

Oral Corticosteroids

- **Prednisone**
- **Prednisolone**

✓ Becuse of their potential for toxicity, they are reserved for patients with severe asthma in which symptoms can not be controlled with safer drugs (eg, inhaled glucocorticoids, beta$_2$ Agonists, theophyline, cromolyn)

✓ Because of the risk of toxicity in long-term usage, treatment should be as brief as posible

Mechanisms of Antiasthmatic Action of Corticosteroids

Glucocorticoids reduce symptoms of asthma by *suppressing inflammation* as a result of the following mechanisms

- ✓ decreased synthesis of inflamatory mediators (eg, leukotriens, histamin, prostaglandin)
- ✓ decreased infiltration and activity of inflamatory cells (eg, eosinophils, leukocytes)
- ✓ decreased edema of the airway mucosa (due to a decrease in vascular permeability)

thereby reducing bronchial hyperactivity.

- ✓ Decrease airway mucus production
- ✓ Increase the number of bronchial $beta_2$ receptors as well as their responsiveness to $beta_2$ agonists.

Mast Cell Stabilizers

- **Cromolyn**
  - ✓ is effective for prophylaxis and the safest of all antiasthma medications
  - ✓ acts by stabilizing the cytoplasmic membrane of mast cells thereby preventing release of histamine

- **Nedocromil**

Leukotriene Receptor Antagonists

- Montelukast (leukotriene receptors blockers)
- Zafirlukast (leukotriene receptors blockers)
- Zileuton (leukotriene synthesis inhibitor)

All of them suppress the effects of leukotriens which are responsible:

- ✓ bronchoconstriction as well as eosinophil infiltration
- ✓ mucus production
- ✓ airway edema,

All drugs are approved for the prophylaxis of asthma.

They can cause elevation in hepatic enzymes

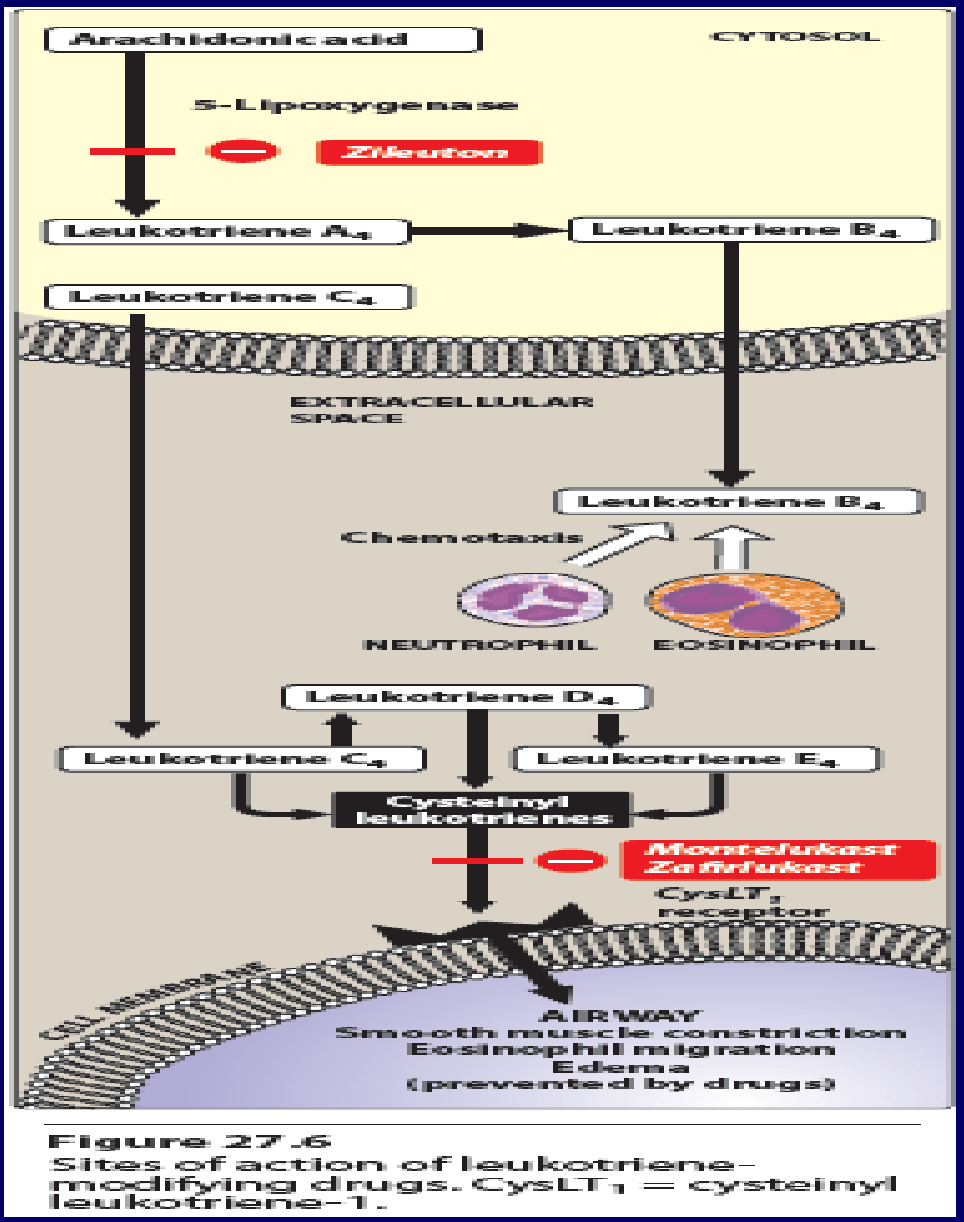


Figure 27.6
Sites of action of leukotriene-modifying drugs. $CysLT_1$ = cysteinyl leukotriene-1.

Biologic Response Modifiers (Monoclonal Antibodies)

❖ Omalizumab

✓ is a second-line agent indicated only for allergy-related asthma.

✓ is administrated subQ.

✓ binds to free IgE in blood thereby reduces the number of IgE molecules on the mast cell and hence limits the ability of allergens to trigger release of histamine, leukotriens and other mediators that promote bronchospasm and airway inflamation.

✓ can only help patients whose asthma is caused by a specific allergen (eg, dust mite feces)

✓ The most severe adverse effects are *malignancy and anaphylaxis* although rare.

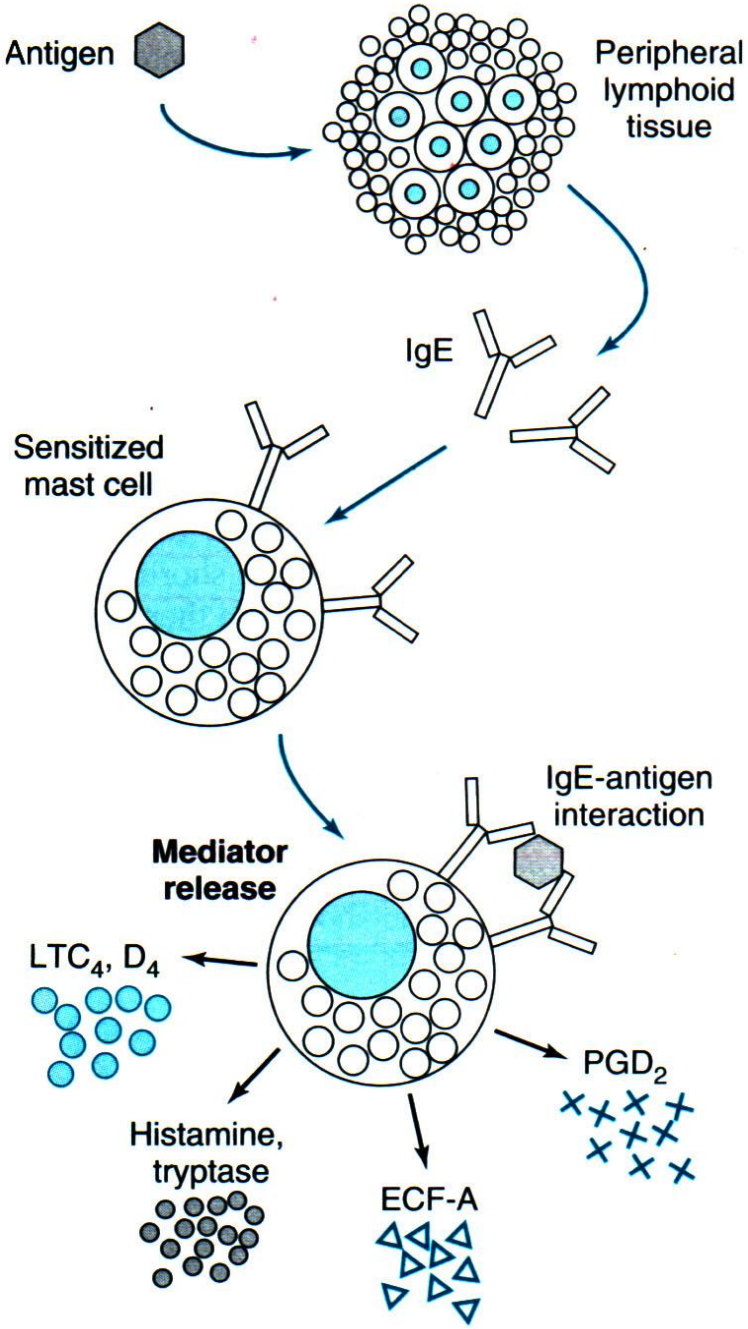


Figure 20–1. Immunologic model for the pathogenesis of asthma. Exposure to antigen causes synthesis of IgE, which binds to and sensitizes mast cells and other inflammatory cells. When such sensitized cells are challenged with antigen, a variety of mediators are released that can account for most of the signs of the early bronchoconstrictor response in asthma. (Modified and reproduced, with permission, from Gold WW: Cholinergic pharmacology in asthma. In: *Asthma Physiology, Immunopharmacology, and Treatment.* Austen KF, Lichtenstein LM [editors]. Academic Press, 1974.)

Admistration of drugs by inhalation has three obvious advantages:

- Therapeutic effects are inhanced because drugs directly reach to their sites of action
- Systemic effects are minimized
- Relief of acute attacks is rapid

Three types of inhalation devices are employed :

- ✓ metered-dose inhalers
- ✓ dry-powder inhalers (Diskus)
- ✓ nebulizer

metered-dose inhalers

Nas•l kullan•l•r ?




/www.allerjim.com/inhalasyon/odi.htm (1 of 2)06.12.2010 10:30:59

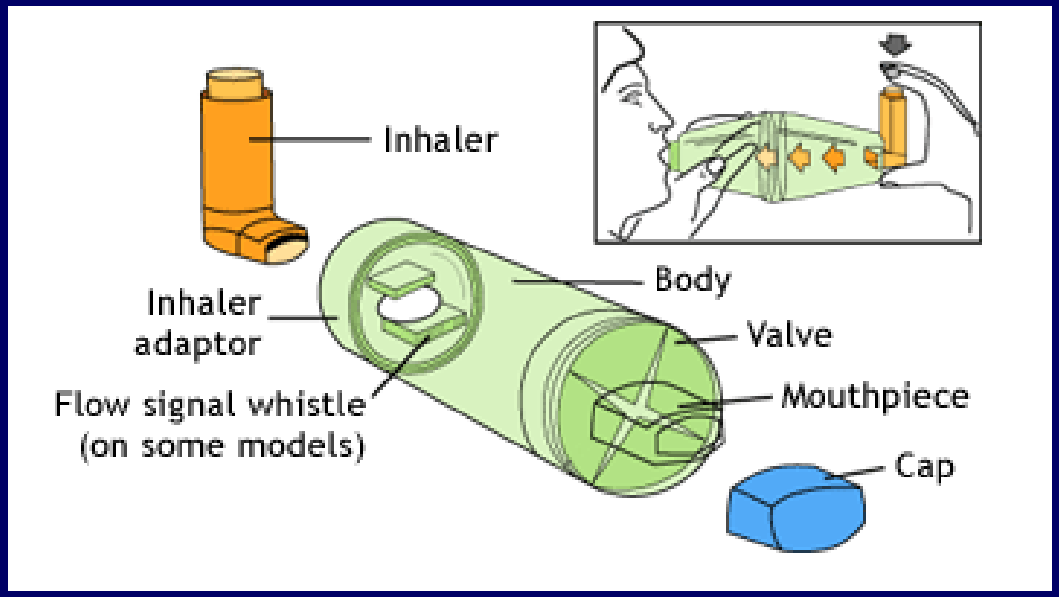
Ölçülü doz inhalerin koruyucu kapa••n• ç•kart•n
•yice çalkalayarak ilaç ve itici gaz•n tamamen kar••mas•n• sa•lay•n
Öncelikle nefesinizi bo•alt•n, cihaz• dudaklar•n•z aras•nda bo•luk kalmayacak •ekilde a•z•n•za yerle•tirin (ba••n•z• hafifçe arkaya e•in)
DER•N fakat YAVA• bir nefes al•rken cihaza bir kez bas•n ve nefes almaya devam edin.
Nefes alma i•lemini tamamlad•ktan sonra cihaz• a•z•n•zdan ay•r•n ve 8-10 saniye nefesinizi tutun.

Kortikosteroid içeren ölçülü doz inhaler kulland•ktan sonra
MUTLAKA
su ile a••z çalkalanmal•
ve gargara yap•lmal•d•r.
(BU SUYU YUTMAYINIZ)

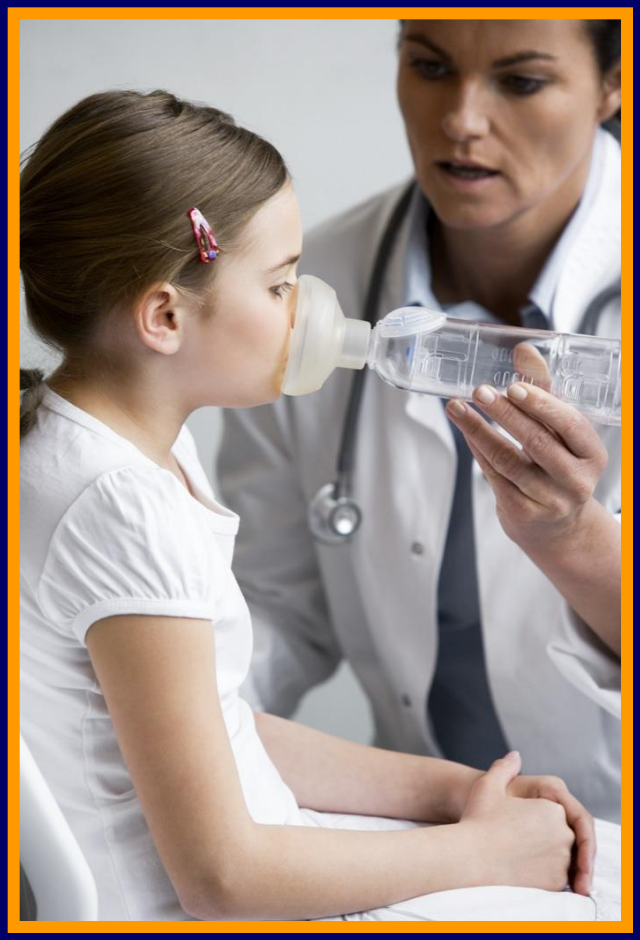
Medications to Treat Asthma: How to Use a Spray Inhaler

The health-care provider should evaluate inhaler technique at each visit.

Source: "What You and Your Family Can Do About Asthma" by the Global Initiative for Asthma Created and funded by NIH/NHLBI


Inhaler
Inhaler adaptor
Flow signal whistle (on some models)
Body
Valve
Mouthpiece
Cap

Medications to Treat Asthma: Inhalers and Spacers



Spacers can help patients who have difficulty with inhaler use and can reduce potential for adverse effects from medication.

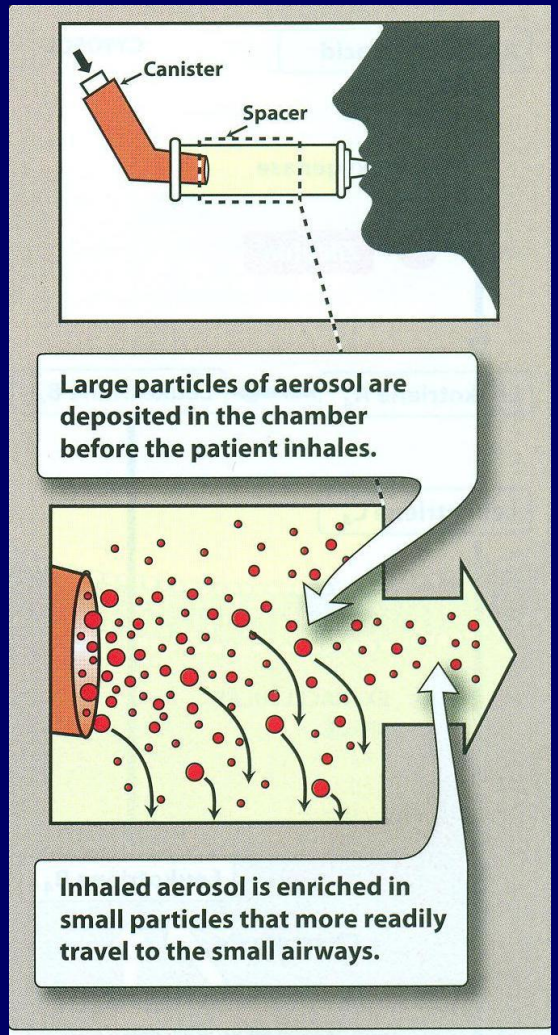


Figure 27.5
Effect of a spacer on the delivery of an inhaled aerosol.

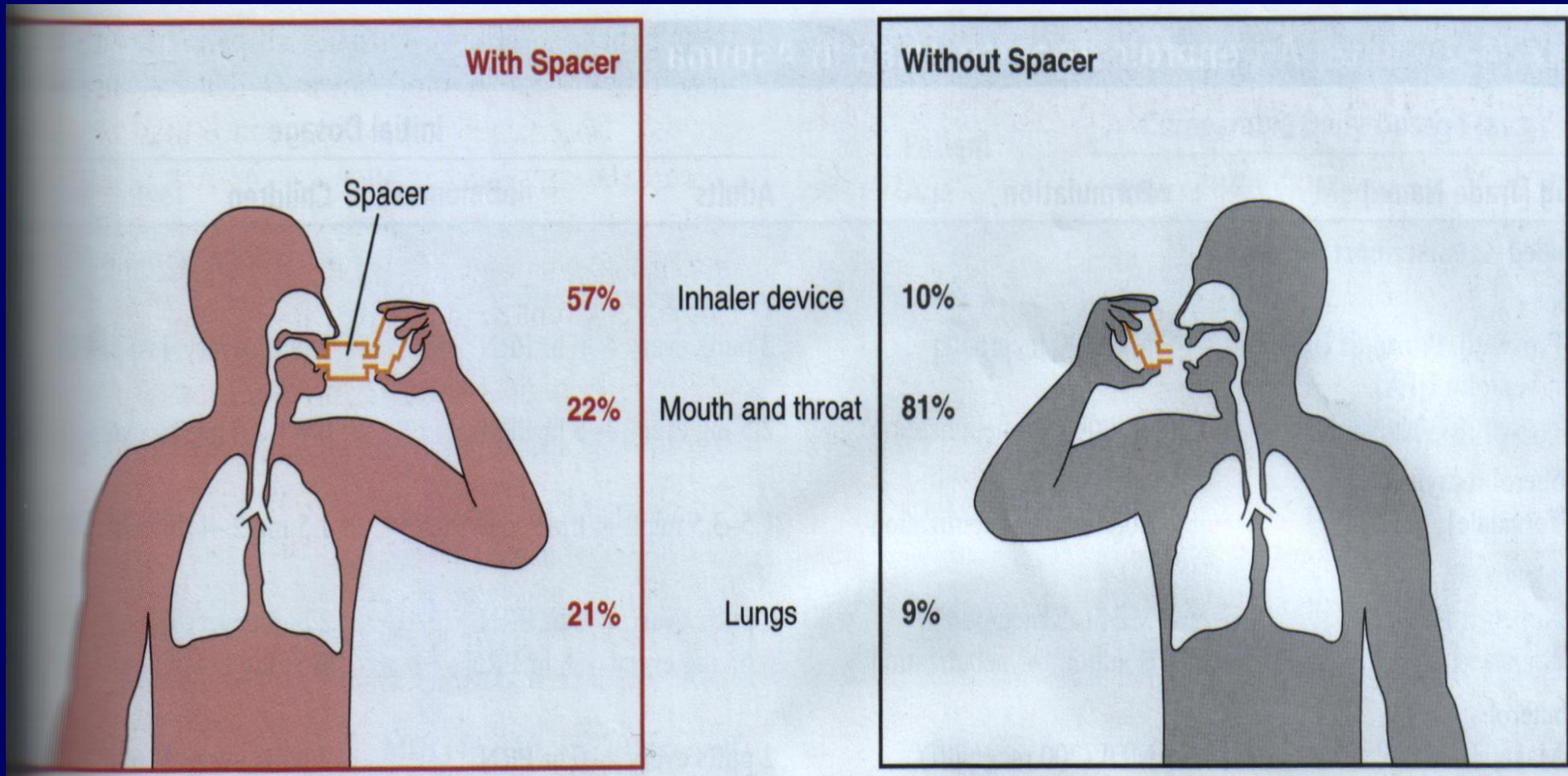


Figure 74–2 ■ Impact of a spacer device on the distribution of inhaled medication. Note that, when a spacer is used, more medication reaches its site of action in the lungs, and less is deposited in the mouth and throat.

Dry-Powdered Inhalers (Diskus)

Nas•l kullan•l•r ?

Solunum hareketi ile (derin nefes alma) diskus içindeki ilaç akci•er hava yollar•na (bron•lara) ula•acakt•r. Bu esnada a•z•n•za laktoz tad• (tatl•) gelecektir. Kullan•m sonras•nda diskusun kapa••n• tekrar kapat•n .

Kortikosteroid içeren diskus kulland•ktan sonra
(Seretide veya Flixotide)
MUTLAKA
su ile a••z çalkalanmal•
ve gargara yap•lmal•d•r.
(BU SUYU YUTMAYINIZ)

Nebulizer

Nebülü aç•n ve a••zl•k ya da yüz maskesinin alt•ndaki ilaç haznesine bo•alt•n. Cihaz• çal••t•r•n.

A••zl••• dudaklar•n•z•n alarak (veya maskeyi yüzünüze kapatarak) yava• ve derin bir •ekilde soluk al•p vermeye ba•lay•n. Ald•••n•z her nefesi 1-2 saniye kadar tutun.

Haznedeki ilaç tamamen bitinceye kadar (10-15 dakika) bu i•leme devam edin.

NEBUL•ZATÖRÜ HER KULLANIMDAN SONRA TEM•ZLEMEK GEREKL•D•R:

1. Maske (veya a••zl•k), ilaç haznesi ve ba•lant• hortumunu birbirinden ay•r•n.
2. Parçalar• •l•k su ile y•kay•n.
3. Parçalar• kurulad•ktan sonra tekrar birle•tirerek, iç yüzeylerin de kurumas•n• sa•lamak için nebülizatörü birkaç dakika çal••t•r•n.
4. Cihaz• bir sonraki kullan•ma kadar kutusunda muhafaza edin.

Kortikosteroid içeren nebul kulland•ktan sonra
MUTLAKA
su ile a••z çalkalanmal•
ve gargara yap•lmal•d•r.
(BU SUYU YUTMAYINIZ)

Medications to Treat Asthma: Nebulizer

- Used for small children or for severe asthma episodes
- No evidence that it is more effective than an inhaler used with a spacer

Poorly controlled asthma leads to:

- Increased visits to
  - Doctor, Urgent Care Clinic or Hospital ER
- Hospitalizations
- Limitations in daily activities
- Lost work days
- Lower quality of life
- Death