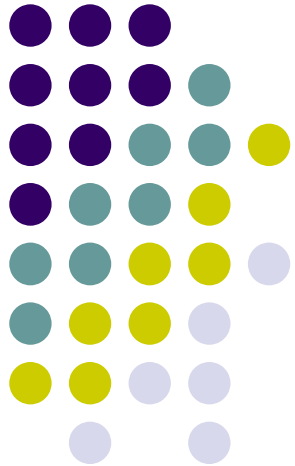
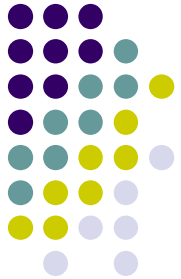
DRUG THERAPY FOR BRONCHIAL ASTHMA



Current Understanding of Asthma



- A chronic inflammatory disorder of the airway
- Infiltration of mast cells, eosinophils and lymphocytes
- Airway hyperresponsiveness
- Recurrent episodes of wheezing, coughing and shortness of breath

Commonest chronic disease in children

& adults.

- inflammatory condition in which there is recurrent reversible airways obstruction in response to irritant stimuli that are too weak to affect non-asthmatic subjects.

- Reversibility of airways obstruction in asthma contrasts with COPD, where obstruction is not reversible or incompletely reversible, by bronchodilators

Control of Bronchial Tone

- **Autonomic Innervation**
  - **Adrenergic stimulation**
  - **β: dilation**
  - **Cholinergic (muscarinic): constriction**

- **Autocoids: released in asthmatic attack (Leukotrienes and Adenosine)**
  - **produce bronchoconstriction**
  - **increase vascular permeability in bronchi and cause mucosal edema**

Drug Treatment of Asthma

What is it ? 'A State of bronchial hyperreactivity resulting from a persistent inflammatory process in response to a number of stimuli in a genetically susceptible individual'

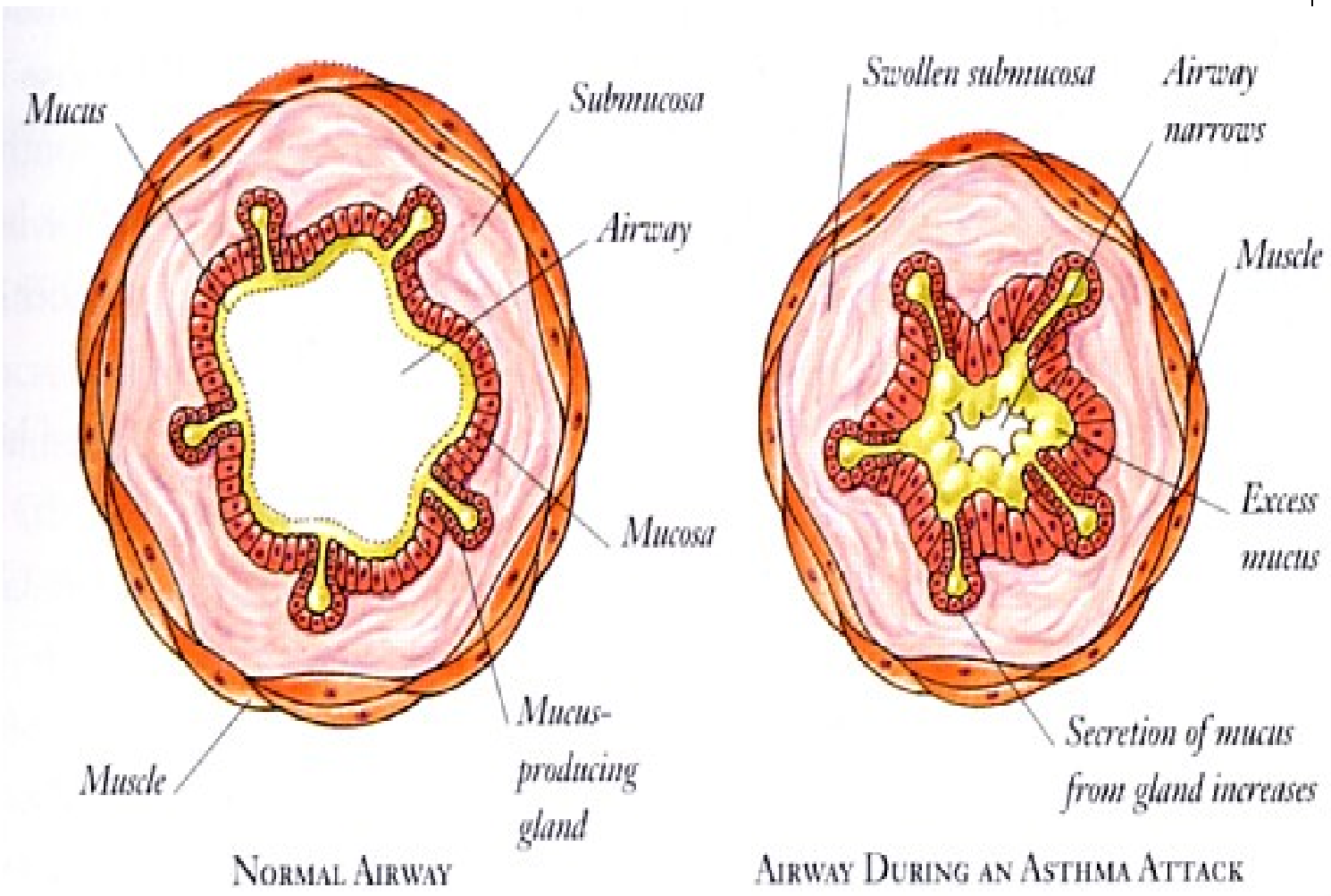
Key features of its pathophysiology

- o mucosal oedema
- o secretion of mucus
- o epithelial damage
- o bronchoconstriction

Therapy is thus aimed at

- **Symptomatic relief** - relieving bronchoconstriction
- **Disease modification** - reducing

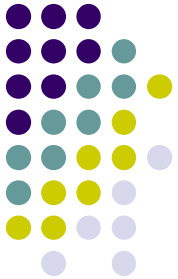
Asthma: Pathological changes



Asthma Triggers

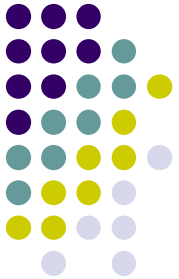
- Allergen exposure e.g. pet dander, pollens etc.
- Exercise/cold-air - drying airway mucosa.
- Drugs
- Food additives - tartrazines , sulphites
- Viral URTIs - especially rhinovirus.

Treatment Goals



- To reverse acute episodes
- To control recurrent episodes
- To reduce bronchial inflammation

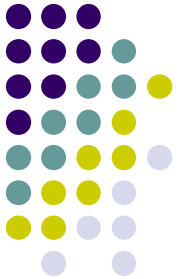
Drugs Used in Asthma



Bronchodilators

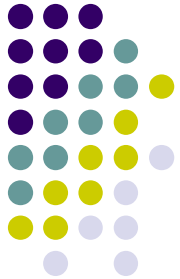
- **Beta-adrenergic agonists relax brochial smooth muscle and decrease microvascular permeabilty**
- **Muscarinic antagonists inhibit the effects of endenous ACh**
- **Theophylline reduce the frequency of recurrent bronchospasm**

Drugs Used in Asthma (con't.)



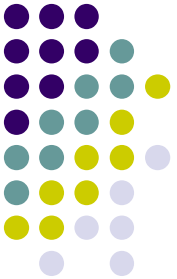
- **Non-bronchodilators (for chronic use)**
  - **Corticosteroids control mucus production and edema**
  - **Cromolyn controls mediator release**
  - **Leucotriene modulators antagonize mediator receptors or decrease their synthesis**

β-ADRENERGIC AGONISTS



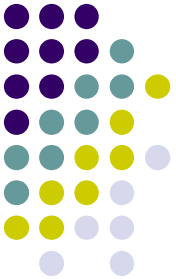
- **Given by inhalation to avoid systemic effects.**
- **are most effective bronchodilators.**
- **↑cyclic AMP in smooth muscle cells↓ tone.**
- **Various drugs differ in their duration of action & receptor selectivity.**
  - **Short-acting (3-6 hr) & β2 selective Albuterol**
  - **Short acting & non-selective: Isoproterenol**
  - **Long-acting (>12 hr) & β2 selective Salmeterol**

β-ADRENERGIC AGONISTS,contd...



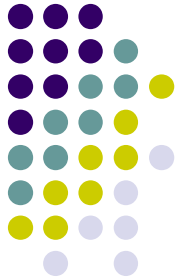
- Useful in prevention of exercise-induced asthma.
- Albuterol like drugs are useful in acute episodes of asthma
- Prolonged acting Salmeterol used in maintenance treatment (prevent nocturnal attacks of asthma)
- Salmeterol has a slow onset of action & is not recommended for acute episodes of asthma.

β-ADRENERGIC AGONISTS contd....



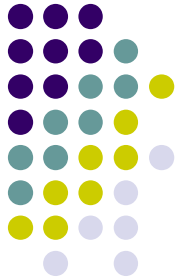
- β-adrenergic agonists have no anti-inflammatory activity.
- Their continuous use may result in desensitization of adrenergic receptors that can be prevented or reversed by corticosteroids
- In high doses these drugs can produce tachycardia, palpitations, and tremor

IPRATROPIUM



- muscarinic receptor antagonist (a synthetic analog of atropine)
- given by inhalation negligible systemic effects
- longer duration of action than adrenergic agonists.
- Used in COPD to decrease cholinergic tone
- Used in asthma in combination with β-adrenergic agonists
- Combination more effective & less toxic than either drug alone
- Has no anti-inflammatory activity

Anti-Muscarinic Agents



- **Competitively inhibits the effect of acetylcholine at muscarinic receptors effectively block the contraction of the airway smooth muscle and increase in secretion of mucus**
- **Ipratropium bromide – a quarternary ammonium derivative of atropine**
- **Delivered by inhalation**
- **Slightly less effective than beta agonist**
- **Effective in COPD**

Methylxanthine drugs

a. caffeine

b. theophylline

c. theobromide

- **Mechanism of action**

  - inhibit the enzyme phosphodiesterase → hydrolyses cyclic nucleotide → result in high concentration of IC cAMP → smooth muscle relaxation

  - inhibition of cell surface receptors for adenosine

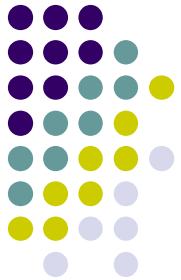
  - anti-inflammatory effect : inhibit the late response of antigenic challenge.

PHARMACOLOGY of METHYLXANTHINES

Theophylline

- stimulate respiratory center (CNS), increases sensitivity of respiratory center to pCO2
- relaxes smooth muscles of the bronchi,
- ineffective by aerosol, given orally
- effective bronchodilator & has slower onset of action than inhaled β2-adren. Agonists.
- proposed mechanisms: adenosine receptor blockade; phosphodiesterase inhibition in high concentration.

Methylxanthines :Theophylline contd.

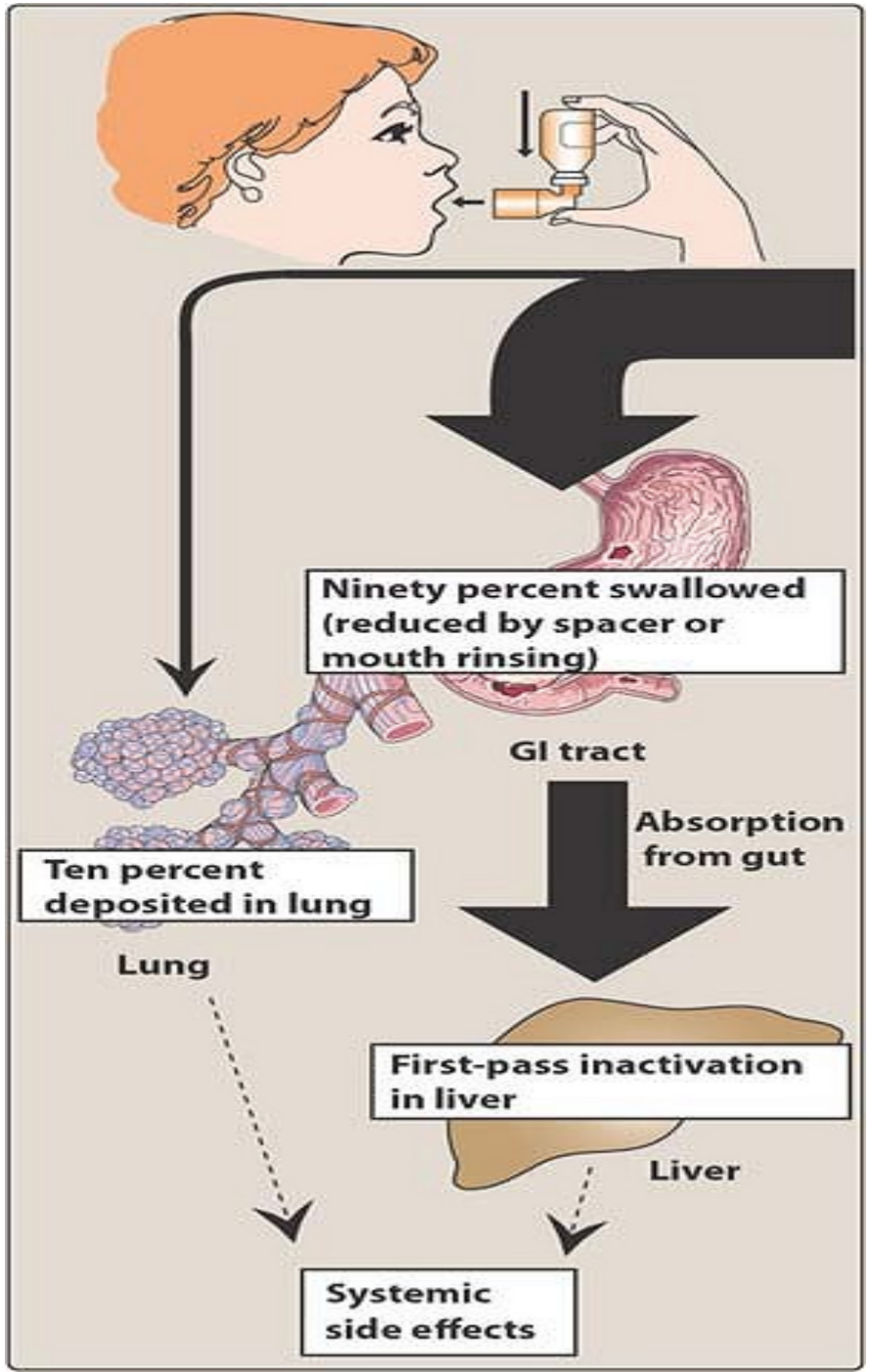


narrow safety index (10-20 ug/ml), its plasma concentration are to be monitored

- Due to its high risk/benefit ratio, it is used as an second line or additional therapy
- Clearance is influenced by smoking, and other drugs metabolized by liver.
- Toxicity is dependent on plasma concentration
  - Mild (30 mg/L): nausea, vomiting, headache, insomnia, and nervousness
  - Potentially serious (40 mg/L): sinus tachycardia
  - Severe (45 mg/L): cardiac arrhythmias, seizures

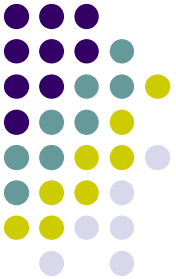
Inhaled steroids

- Most widely used are beclamethasone & budesonide.
- Both are potent & absorbed from GIT and partial first-pass metabolism in liver
- When used up to 1000 µg –day no adrenocortical function effects
- Fluticasone propionate highly selective, poorly absorbed from GIT, subject to 100% first pass metabolism in liver. Safer in children



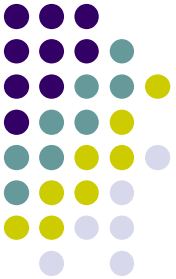
Pharmacokinetics of inhaled glucocorticoids

INHALED CORTICOSTEROIDS

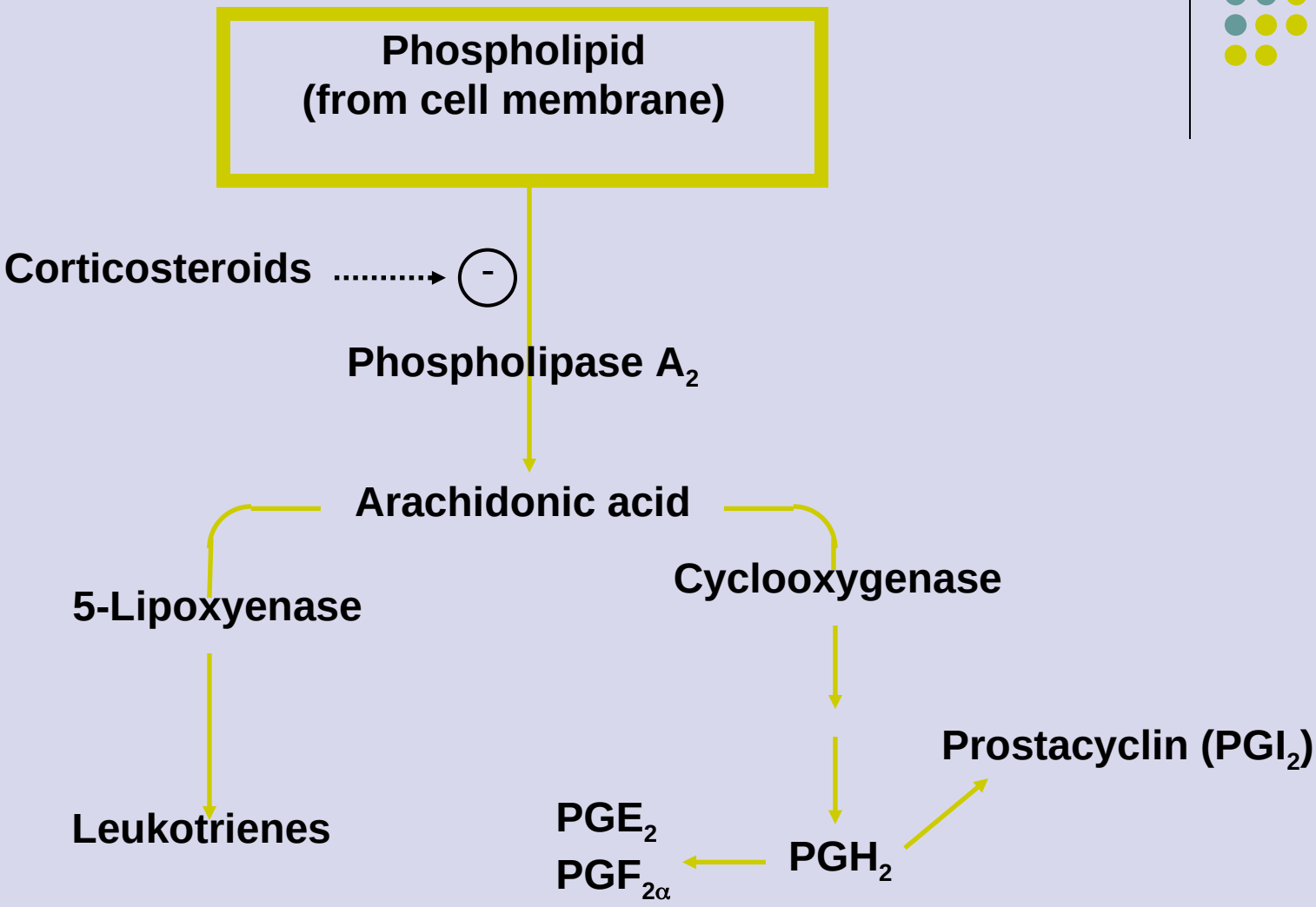


- **decrease inflammation & edema in respiratory tract**
- **inhibit phospholipase A2 through synthesis of lipocortin,**
- **block release of arachidonic acid and its metabolites (leukotrienes)**
- **also inhibit production pro-inflammatory cytokines**
- **Used in chronic asthma, lowers the frequency of acute episodes**
- **are not bronchodilators & are not useful acute attacks**
- **May cause dysphonia and/or esophageal candidiasis**

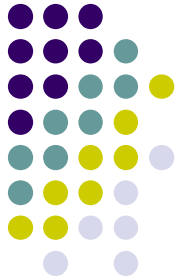
Side effects of inhaled steroids



- Depression of adrenocortical function
- Effects on bone metabolism
- Effects of growth in children
- Easy bruising & skin thinning
- Cataract formation


Phospholipid
(from cell membrane)
Corticosteroids
-
Phospholipase A_2
Arachidonic acid
5-Lipoxyenase
Cyclooxygenase
Leukotrienes
PGE_2
$PGF_{2\alpha}$
PGH_2
Prostacyclin (PGI_2)

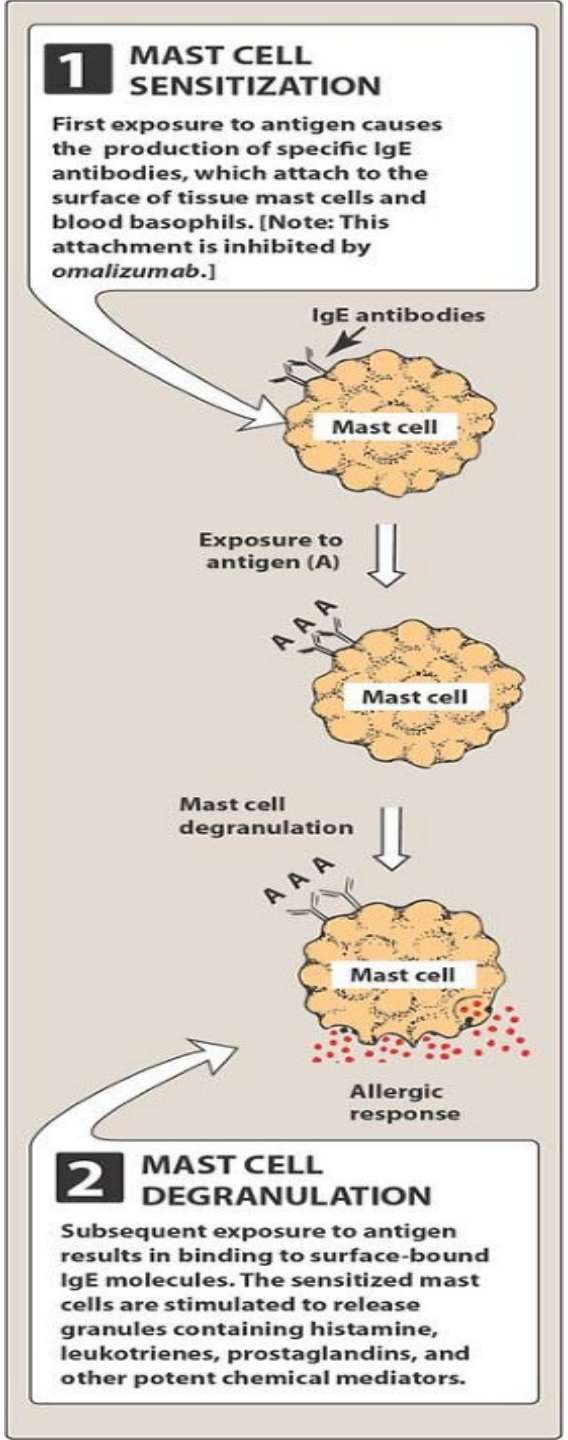
SYSTEMIC CORTICOSTEROIDS (Prednisone)



- **Oral (or injected) steroids are most effective drugs for asthma, unresponsive to bronchodilators and inhaled steroids.**
- **After recovery from severe exacerbation, oral corticosteroids are continued for 8 to 10 days**
- **Alternate-day use decreases adverse effects**
- **Potential adverse effects: glucose intolerance, sodium and water retention, increased BP, peptic ulcer, osteoporosis, cataract, immuno-suppression, ACTH-suppression**

CROMOLYN SODIUM

- stabilizes mast cells & decreases airway responsiveness to spasmogens
- useful for prophylaxis only
- not effective in all patients
- more effective in children and adolescents than in older patients
- may take up to 4-6 weeks of its treatment to be effective in chronic asthma
- has no bronchodilating activity
- has virtually no toxicity


1 MAST CELL SENSITIZATION
First exposure to antigen causes the production of specific IgE antibodies, which attach to the surface of tissue mast cells and blood basophils. [Note: This attachment is inhibited by omalizumab.]
IgE antibodies
Mast cell
Exposure to antigen (A)
A A A
Mast cell
Mast cell degranulation
A A A
Mast cell
Allergic response
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.

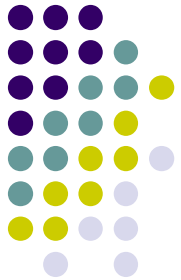
Leukotriene Modulators:

Two types:

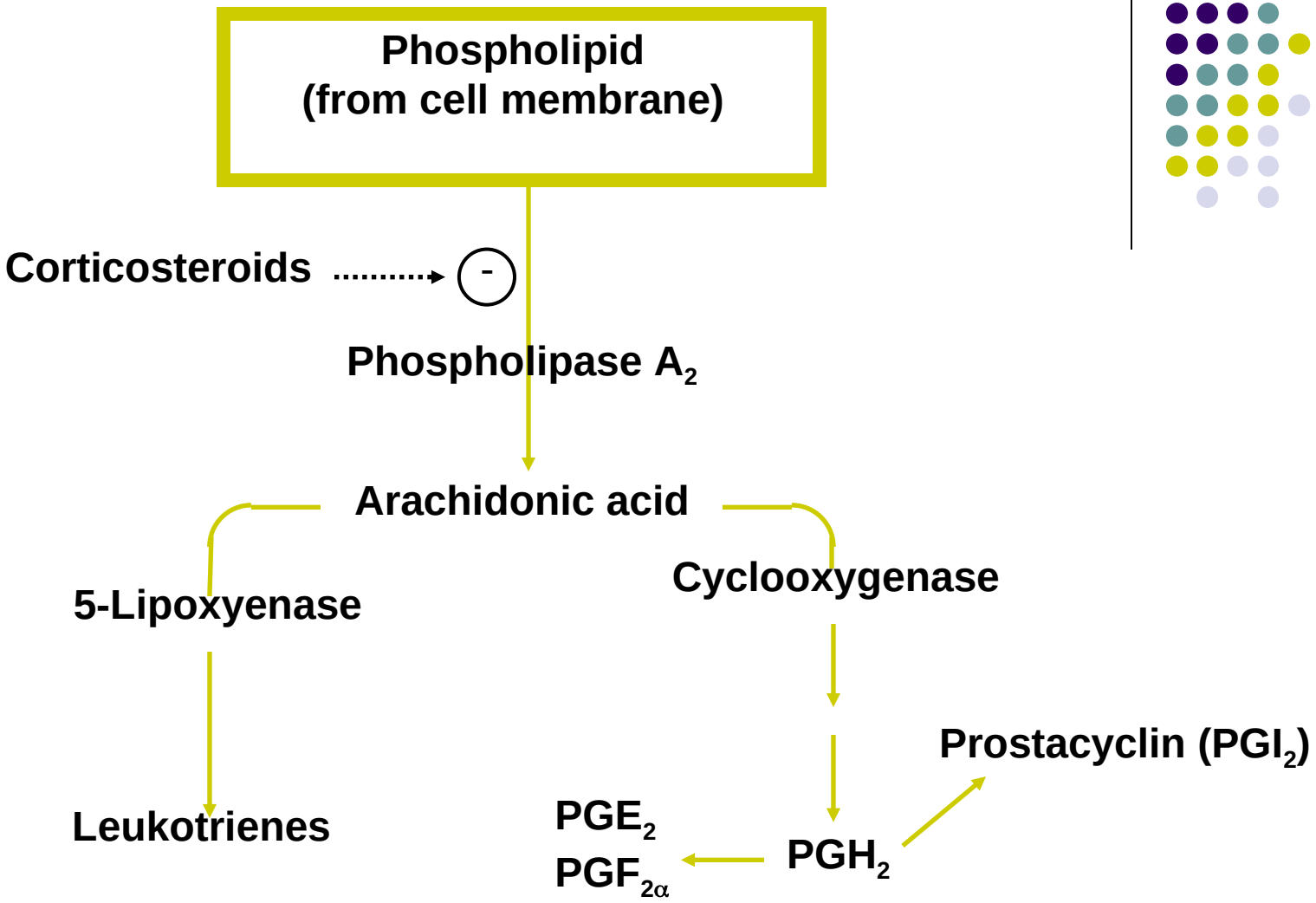
1. **LT receptor antagonists: Montelukast , Zafirlukast)**
2. **Inhibitors of LT synthesis: inhibit 5-lipoxygenase, prevent conversion of arachidonic acid to leukotrienes: Zileuton**

- **Are not bronchodilators & not useful in acute episodes of asthma**
- **Reduce frequency of acute episodes**

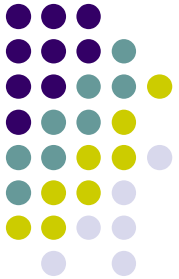
Leukotriene Modulators (cont'd)



- Less effective antiinflammatory agents than corticosteroids
- Used orally, useful in children in chronic treatment of mid to moderate asthma
- generally well tolerated
- Zileuton can elevate liver enzymes
- Zileuton increase plasma concentrations of theophylline and warfarin because it inhibits cytochrome P450 enzymes in the liver.

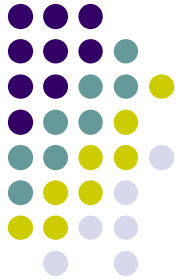

Phospholipid
(from cell membrane)
Corticosteroids
-
Phospholipase A_2
Arachidonic acid
5-Lipoxyenase
Cyclooxygenase
Leukotrienes
PGE_2
$PGF_{2\alpha}$
PGH_2
Prostacyclin (PGI_2)

Various severities of asthma



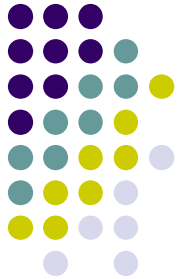
- Step-wise pharmacotherapy treatment program for varying severities of asthma
  - Mild Intermittent (Step 1)
  - Mild Persistent (Step 2)
  - Moderate Persistent (Step 3)
  - Severe Persistent (Step 4)

Mild Intermittent Asthma



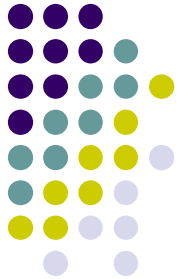
- Day time symptoms ≤ 2 times a week
- Night time symptoms ≤ 2 times amonth
- PEF or FEV1 ≥ 80% of predicted
  - PEF and FEV1 values are only for adults and for children over the age of 5
  - No daily medication needed
  - short-acting bronchodilator (albuterol) MDI as and when required
  - Severe exacerbations may require systemic corticosteroids

Mild Persistent Asthma



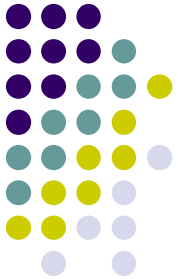
- Day time symptoms > 2/week, but < 1/day
- Night time symptoms < 1 night / week
- PEF or FEV1 ≥ 80% of predicted
- **Step 2 (Mild persistent)**
  - Preferred Treatment
    - Low-dose inhaled corticosteroid daily
  - Alternative Treatment (no particular order)
    - Cromolyn
    - Leukotriene receptor antagonist
    - Nedocromil
    - Sustained release theophylline to maintain a blood level of 5-15 mcg/mL

Moderate Persistent Asthma



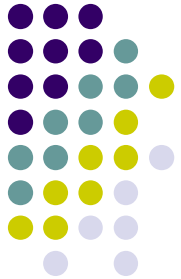
- Day time symptoms whole day
- Night time symptoms > 1 night / week
- PEF or FEV1 60%-80% of predicted
- **Step 3 (Moderate persistent)**
  - Preferred Treatment
    - Low-to-medium dose inhaled corticosteroids
    - WITH long-acting inhaled beta2-agonist
  - Alternative Treatment
    - Increase inhaled corticosteroids within the medium dose range
    - Add leukotriene receptor antagonist or theophylline to the inhaled corticosteroid

Severe Persistent Asthma



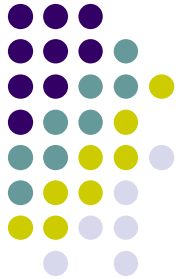
- Day time symptoms: continual
- Night time symptoms: frequent
- PEF or FEV1 ≤ 60% of predicted
- **Step 4 (Severe persistent)**
  - Preferred Treatment
    - High-dose inhaled corticosteroids
    - AND long-acting inhaled beta2-agonists
    - AND (if needed) oral corticosteroids

Pharmacotherapy for Infants and Young Children (<5 years)



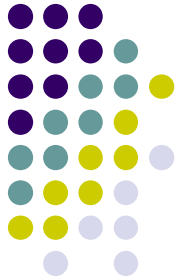
- Step 1(mild intermittent)
  - No daily medication needed

Pharmacotherapy for Infants and Young Children (<5 years)



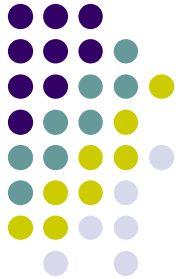
- Step 2 (mild persistent)
  - Preferred treatment
    - Low-dose inhaled corticosteroids
  - Alternative treatment
    - Cromolyn (nebulizer preferred)
    - OR leukotriene receptor antagonist

Pharmacotherapy for Infants and Young Children (<5 years)



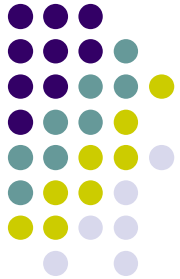
- Step 3 (moderate persistent)
  - Preferred treatment
    - Low-dose inhaled corticosteroids and long-acting beta2-agonist
    - OR Medium-dose inhaled corticosteroids
  - Alternative treatment
    - Low-dose inhaled corticosteroids with either:
    - Leukotriene receptor antagonist
    - OR theophylline

Pharmacotherapy for Infants and Young Children (<5 years)



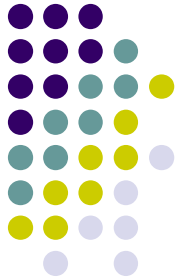
- Step 4 (severe persistent)
  - Preferred treatment
    - High-dose inhaled corticosteroids
    - AND long-acting inhaled beta2-agonist
    - AND (if needed) Oral corticosteroids
  - For young children, inhaled medications should be given by nebulizer, dry powder inhaler (DPI), or MDI with a chamber/spacer

Acute Exacerbations



- Inhaled albuterol is the treatment of choice in absence of impending respiratory failure
- MDI with spacer as effective as nebulizer with equivalent doses
- Adding an antibiotic during an acute exacerbation is not recommended in the absence of evidence of an acute bacterial infection

Exercise-induced Bronchospasm



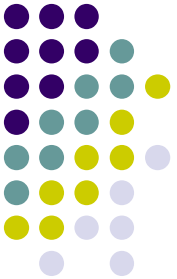
- Short acting Beta Agonist are best pre-treatment

Table 37-1

RECOMMENDATIONS FOR PHARMACOLOGIC MANAGEMENT OF ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5

ASTHMA SEVERITY	SYMPTOM FREQUENCY	MEDICATIONS
Mild intermittent	<2 days/week, <2 nights/month	None; course of systemic glucocorticoids for occasional, severe exacerbations
Mild persistent	>2 per week but <once per day >2 nights/month	Low-dose inhaled glucocorticoids. Alternate: cromolyn, nedocromil, leukotriene modifier, *or* sustained release theophylline
Moderate persistent	Daily, >1 night/week	Low- to medium-dose glucocorticoids and long-acting inhaled β_2-agonists. Alternate: leukotriene modifier or theophylline
Severe persistent	Continual during day, frequent at night	High-dose glucocorticoids *and* long-acting inhaled β_2-agonist *and* (if needed) systemic glucocorticoids

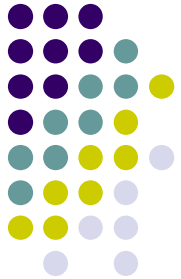
ACUTE SEVERE ASTHMA (STATUS ASTHMATICUS)



This is a life-threatening emergency

recommendations of the British Thoracic Society

Immediate treatment

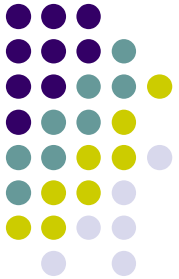


- *Oxygen by mask (humidified, to help liquefy*mucus).
- *Salbutamol by nebuliser in a dose of 2.5-5 mg* over about 3 min, repeated in 15 min.
- *Terbutaline* 5-10 mg is an alternative.
- *Prednisolone 30-60 mg p.o. or hydrocortisone* 200 mg i.v.
- *Avoid sedation of any kind.*
- Chest x-ray to exclude pneumothorax

If life-threatening features are present (absent breath sounds, cyanosis, bradycardia, exhausted appearance or PEFR < 30% predicted.

- *Ipratropium 0.5 mg should be added to the* nebulised B2-agonist.
- Give i.v. either *salbutamol 250 microgram over*10 minutes (as nebulised salbutamol may not be reaching the distal airways) or *aminophylline 5 mg/kg.*
- *Aminophylline should not be given to* patients already taking oral theophyllines.
- Alert the intensive care unit

Subsequent management



If the patient is improving,

- continue: 40-60% oxygen
- Prednisolone 30-60 mg daily or hydrocortisone 200 mg 6-hourly
- Nebulised salbutamol or terbutaline 4-hourly.

If the patient is not improving after 15-30 minutes:

- Continue oxygen and glucocorticoid
- Give nebulised (B2-adrenoceptor agonist more frequently, up to every 15-30 minutes
- Add ipratropium 0.5 mg to nebuliser and repeat 6-hourly until patient is improving.

If the patient is still not improving give:

- i.v. infusion of [B2-adrenoceptor agonist or aminophylline (0.9 microgram/kg/min)
- i.v. infusion of a (B2-adrenoceptor agonist (as above) as an alternative
- Contact the intensive care unit to discuss

intubation and mechanical ventilation.

- **Monitoring response to treatment**
- By peak expiratory flow rate (PEFR) every 15-30 minutes
- Oxygen saturation: maintain > 92%

- Drugs which predispose to asthma

BETA BLOCKERS

NSAIDS esp aspirin