

ASTHMA

# PHARMACOTHERAPY OF ASTHMA

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# ASTHMA DEFINATION

“Asthma is defined as a chronic inflammatory disease of airway that is characterized by increase responsiveness of tracheobronchial tree to a multiplicity of stimuli .”

Extrinsic: episodic, atopy

Intrinsic : perennial, status asthmaticus

# Asthma is characterised

CLINICALLY- Recurrent bouts of coughing, shortness of breath, chest tightness & wheezing

PHYSIOLOGICALLY- Narrowing of bronchial airway & increase in bronchial responsiveness

PATHOLOGICALLY- Lymphocytic eosinophilic inflammation of bronchial mucosa Remodelling of bronchial mucosa & hyperplasia of all structural elements

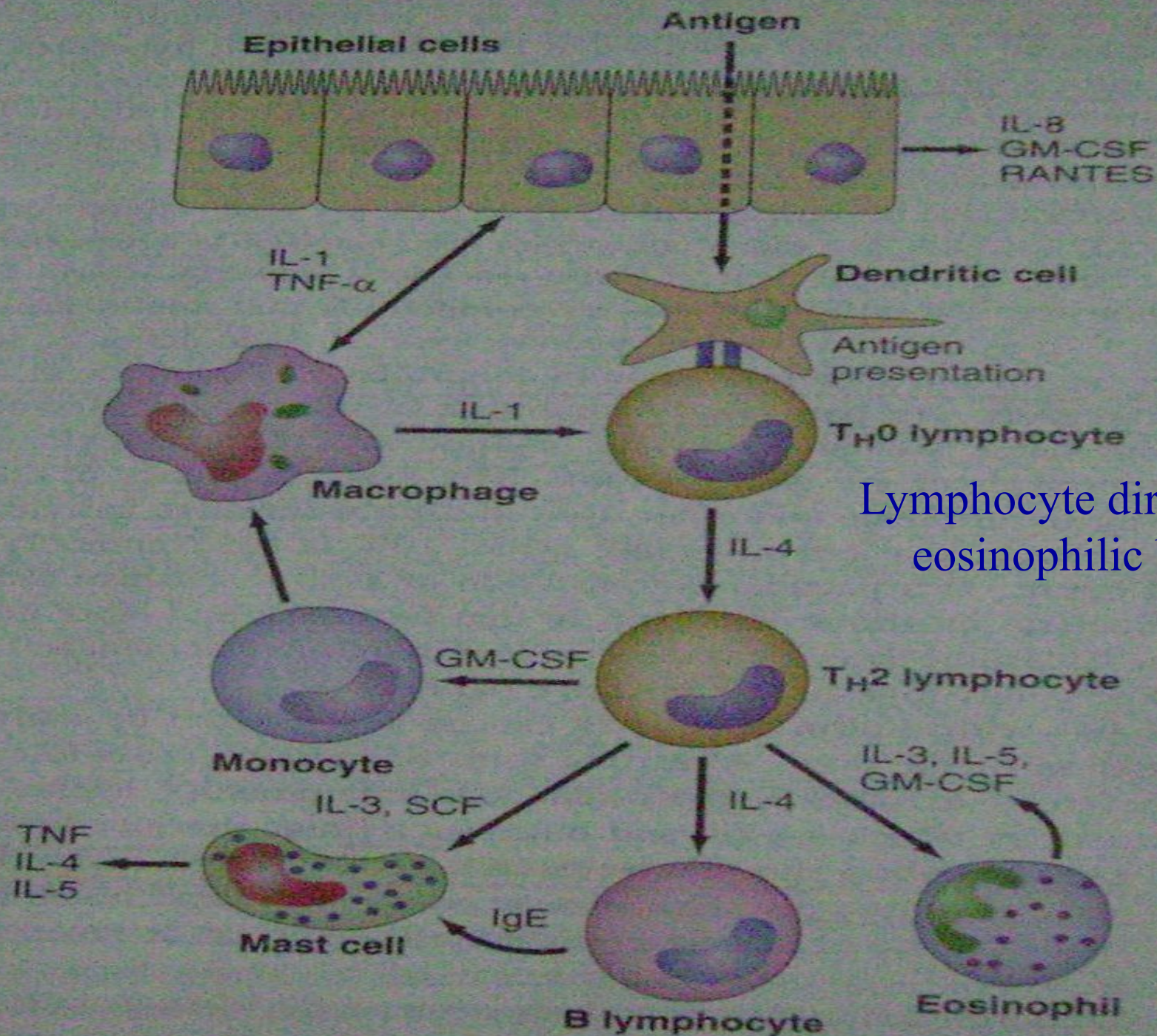
# PATHOGENESIS OF ASTHMA

## ASTHMA AS AN INFLAMMATORY ILLNESS

↑ no. of inflammatory cells (eosinophils)

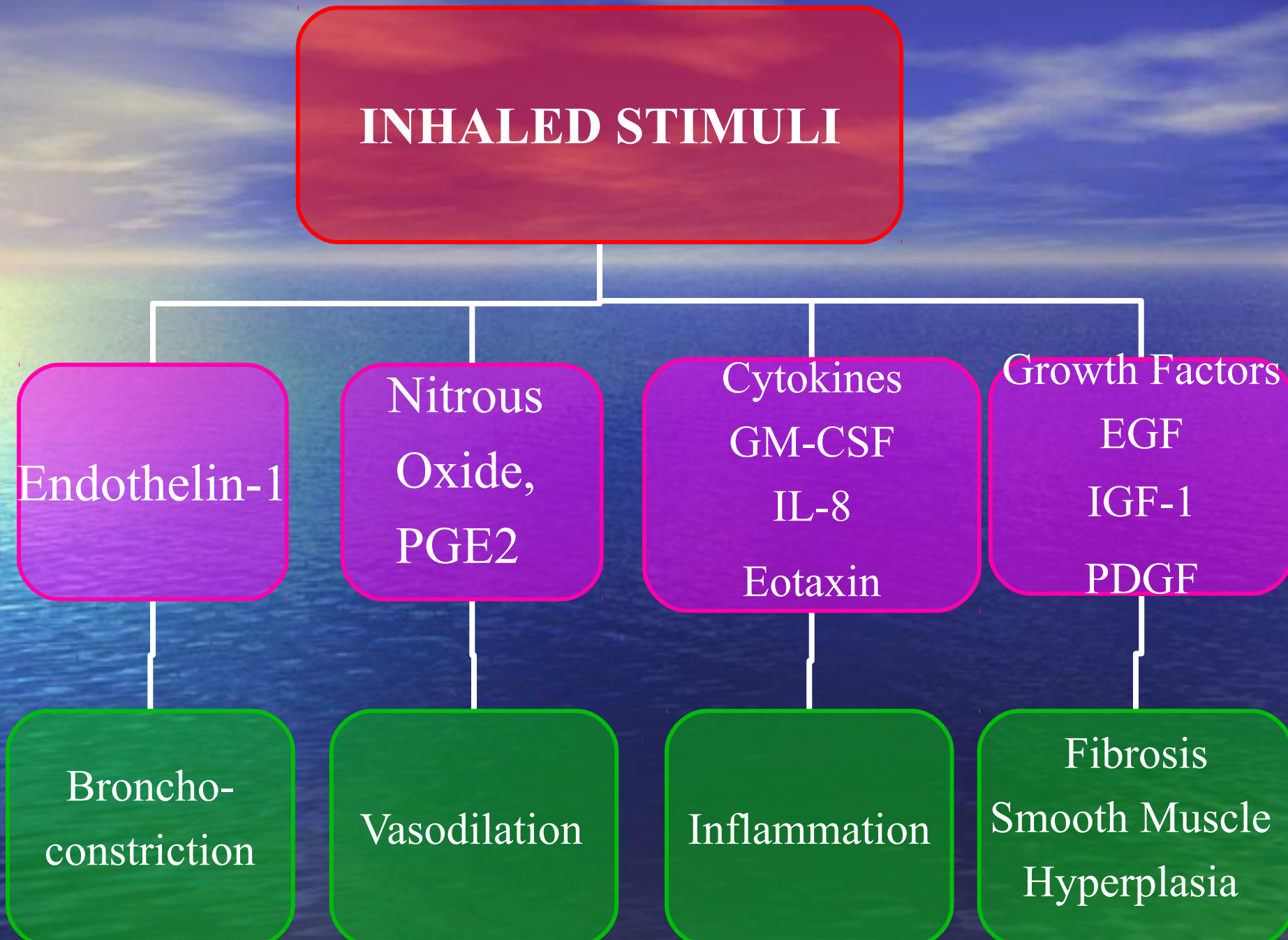
These produces mediators as

- Mediators stored in granules (immediate)-  
Histamine, Protease enzymes,  $\text{TNF-}\alpha$
- Membrane phospholipids f/b mediator synthesis  
(within minutes) - PGs, LTs, PAF
- Gene activation f/b protein synthesis (over hrs)- ILs,  
 $\text{TNF-}\alpha$



Lymphocyte directed  
eosinophilic bronchitis

# INHALED STIMULI



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graph TD; A[INHALED STIMULI] --> B[Endothelin-1]; A --> C[Nitrous Oxide, PGE2]; A --> D["Cytokines<br/>GM-CSF<br/>IL-8<br/>Eotaxin"]; A --> E["Growth Factors<br/>EGF<br/>IGF-1<br/>PDGF"]; B --> F[Broncho-constriction]; C --> G[Vasodilation]; D --> H[Inflammation]; E --> I["Fibrosis<br/>Smooth Muscle<br/>Hyperplasia"];
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The diagram is a hierarchical flowchart set against a background of a blue sky with clouds. At the top is a red rounded rectangle labeled 'INHALED STIMULI'. A white line descends from this box and branches into four vertical lines, each leading to a purple rounded rectangle. These purple boxes contain lists of stimuli: 'Endothelin-1', 'Nitrous Oxide, PGE2', a list of cytokines (GM-CSF, IL-8, Eotaxin), and a list of growth factors (EGF, IGF-1, PDGF). From each purple box, a white line descends to a green rounded rectangle. These green boxes represent the physiological effects: 'Broncho-constriction' (from Endothelin-1), 'Vasodilation' (from Nitrous Oxide, PGE2), 'Inflammation' (from the cytokines), and a list of effects (Fibrosis, Smooth Muscle, Hyperplasia) (from the growth factors).

Endothelin-1

Broncho-  
constriction

Nitrous  
Oxide,  
PGE2

Vasodilation

Cytokines  
GM-CSF  
IL-8  
Eotaxin

Inflammation

Growth Factors  
EGF  
IGF-1  
PDGF

Fibrosis  
Smooth Muscle  
Hyperplasia

# INVESTIGATIONS

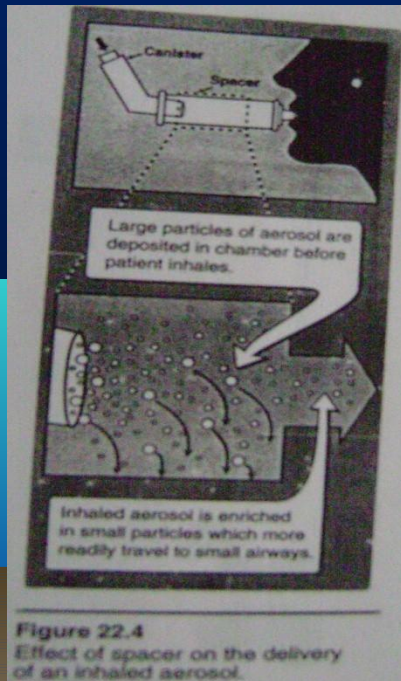
1. Pulmonary Function Test – PEFR, FEV1 etc.
2. Absolute eosinophil count
3. Chest X-ray
4. Allergy test

# Approaches to treatment

1. Prevention of AG:AB reaction- AG avoidance  
Hyposensitization
2. Neutralization of IgE- Omalizumab
3. Supression of inflammation & bronchial hyperreactivity-  
corticosteroids
4. Prevention of release of mediators- mast cell stabilizers
5. Antagonism of related mediators- LT antagonist,  
antihistamines, PAF antagonist
6. Blockade of constrictor NT- Anticholinergics
7. Mimicking dilator NT- Sympathomimetics
8. Directly acting bronchodilator- Methyl xanthines

# AEROSOL DELIVERY OF DRUG

- High local conc.-↓systemic side effects
- Delivery to Lung- Particle size 1-5 $\mu$ m
- Other factors- Rate of breathing & breath holding
- Maneuvers that ↑ drug deposition in lung
- Spacer - ↑ inhaled : swallow drug



## Using an Inhaler

Definitions: MN Dept. of Health

**Spacer:** a device that is attached to a Metered-Dose Inhaler (MDI). The spacer extends the distance between the inhaler and the mouth. The spacer slows down the movement of medication particles and directs them as they come out of the MDI. This allows more of the medication to reach the lungs.



# INHALATION DELIVERY SYSTEM

- MDI (Pressurized Metered Dose Inhaler) :-
  - CFC propellants
  - HFA propellants
  - Cheap portable – Hand breathing co-ordination
- NEBULIZER :-
  - two types – ultrasonic & jet
  - not req. handbreathing co-ordination
  - Severe asthma exacerbation
  - face mask- children & older pt.
  - ultrasonic- hypertonic saline



## Using an Inhaler

Definitions: MN Dept. of Health

**Metered Dose Inhaler (MDI):** a device used to take asthma medications. A dose of the medication is released as you push down on the canister of the inhaler. The medication is inhaled directly into the lungs.

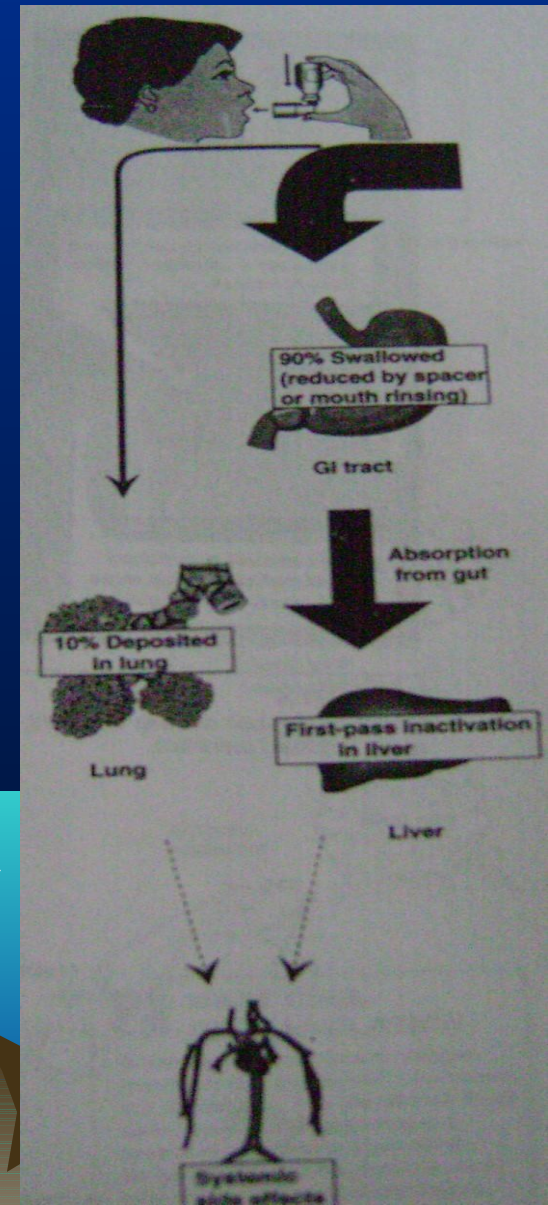


- DRY POWDER INHALER :- Spinhaler & Rotahaler

- Lactose or Glucose
- High air flow req.
- Irritating , Storage –humidity

## FATE OF DRUG

- Only small % deposited 2-10%
- Swallowed drug –First pass metabolism



# CLASSIFICATION

## **I) BRONCHODILATORS :**

- A)  $\beta$ -2 Sympathomimetics:- Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol
- B) Methyl Xanthines:- Theophylline, Aminophylline, Choline-theophyllinate, Hydroxyethyl Theophylline, Doxophylline
- C) Anticholinergics :– Ipratropium bromide, Tiotropium bromide

## **II) LEUKOTRIEN ANTAGONISTS :**

Montelukast, Zafirlukast, Zileuton

## **III) MAST CELL STABILIZERS :**

Na cromoglycate, Nedocromil, Ketotifen

## **IV) CORTICOSTEROIDS :**

- A) Systemic: Hydrocortisone, Prednisolone etc
- B) Inhalational: Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide

## **V) ANTI IgE ANTIBODY : Omalizumab**

# I) BRONCHODILATORS

## A} $\beta$ -2

### SYMPATHOMIMETICS

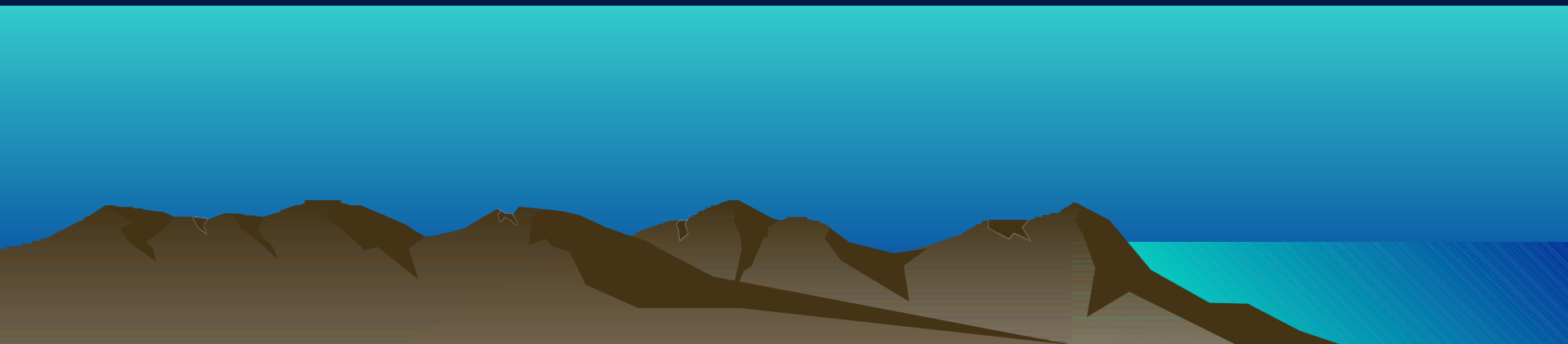
- ▶ SHORT ACTING - Symptomatic relief
- ▶ LONG ACTING - Prophylactic t/t

### MECHANISM OF ACTION

- ▶ Stimulation of  $\beta$ -2 receptors  $\rightarrow$   $\uparrow$ c-AMP formation in bronchial smooth muscle  $\rightarrow$  relaxation of smooth muscle.  $\uparrow$ conductance of large  $\text{Ca}^{+2}$  sensitive  $\text{K}^{+}$  channels  $\rightarrow$  membrane hyper polarization & relaxation
- ▶ Stimulation of  $\beta$ -2 receptors on inflammatory cells  $\rightarrow$   $\uparrow$ intracellular c-AMP  $\rightarrow$  inhibit release of mediators & cytokines

# Receptor Desensitization:-

- ▶ chronic t/t ,
- ▶ Receptor on bronchial smooth muscles → resistant
- ▶ Receptor on inflammatory cells → desensitized rapidly.
- ▶ Little effective in inhibiting airway inflammation.



# SHORT ACTING $\beta$ -2 ADRENERGIC AGONISTS

Albuterol(salbutamol), Levoalbuterol,  
Metapreterenol, Terbutaline, Pirbuterol,  
Isoetharine, Bitolterol, Fenoterol, Procaterol

- Inhalation, onset action within 1-5 min.

- Bronchodilation for 2-6 hrs.

- Most effective drug → reversing  
Bronchoconstriction

- Rapid symptomatic relief; as needed basis

## i] **ALBUTEROL(SALBUTAMOL):-**

- Attack of asthma
- S/E – Muscle tremors, palpitation restlessness, nervousness, ankle edema, throat irritation
- Presystemic metabolism in gut wall
- Dose- 2-4mg oral, 100-200 $\mu$ g inhalation, 0.25-0.5mg im/s.c.

## ii] **LEVOALBUTEROL(LEVOSALBUTAMOL):-**

- R-enantiomer of albuterol
- more potent Bronchodilator
- less side effects: so used in pt with h/o SVT & other arrhythmias

## iii]

**TERBUTALINE:-** Similar to albuterol

Dose 5mg oral, 0.25mg sc, 250 $\mu$ g inhalation

#### **iv] METOPROTERENOL:-**

- Less  $\beta_2$  selective
- resistant to methylation by COMT
- More prone to cardiac stimulation

#### **v] ISOETHARINE:-**

- First  $\beta_2$  selective widely used
- resistant to metabolism by MAO
- Inhalation

**vi] FENOTEROL :-** Association with increase death

**vii] BITOLTEROL:-** Prodrug - esterases hydrolyzes to active Colterol

**viii] ~~PIRBUTEROL~~ & ix] PROCATEROL :-** Inhalation

# LONG ACTING $\beta$ -2 ADRENERGIC AGONISTS

SALMETEROL, FORMOTEROL,  
BAMBUTEROL, CLENBUTEROL

## i) SALMETEROL:-

- First long acting  $\beta$ 2 agonist
- slow onset of action
- duration is 12 hrs bronchodilation
- inhalation twice daily - nocturnal asthma
- 10,000 more lipophilic than albuterol
- unbound salmeterol persist in membrane & slowly dissociate from receptor environment
- DOSE: 50-100  $\mu$ g BD by inhalation

ii) **FORMOTEROL:-**

- Fast onset of action, duration 12 hrs
- DOSE: 12-24  $\mu\text{g}$  BD by inhalation

iii) **BAMBUTEROL:-**

- Prodrug of terbutaline
- Hydrolyzed by pseudo cholinesterase-release active drug
- Chronic bronchial asthma
- DOSE: 10-20 mg OD in evening orally

iv) **CLENBUTEROL:-**

- More potent, long acting & thermogenic drug
- $\uparrow$  aerobic capacity,  $\uparrow$  BP, CNS Stimulation
- $\uparrow$  fat & protein use  $\downarrow$  glycogen storage – wt. loss drug
- banned for athletes & players
- DOSE: 20-60 $\mu\text{g}$ /day max. 150 $\mu\text{g}$

## ORAL THERAPY:-

- Greater risk of side effects- Tremors, muscle cramps, cardiac tachyarrhythmia & metabolic disturbances
- two situations of oral therapy
  1. Young children (syr.) -can not manipulate inhalers
  2. Severe asthma exacerbation- local irritation

## COMBINATION —

- Long acting  $\beta_2$  agonist + Glucocorticoids
- Salmeterol + Fluticasone, Formoterol + Budesonide
- More effective than doubling steroid dose
- Current guideline- medium/low doses of steroids

## B} METHYL XANTHINES

- Theophylline - first extracted from tea leaves
  - 1888 by German biologist Albrecht Kossel.
- Synthesized by another German scientist, Wilhelm Traube.
- First clinical use in asthma t/t in 1950s.
- Among Least expensive
- Three xanthine alkaloids: Caffeine, Theophylline & Theobromine

# PHARMACOLOGICAL

## ACTIONS:

- 1) CNS: Stimulation ↑ performance & motor activity caffeine  
Higher doses (Theophylline) - nervousness, insomnia, delirium, convulsion vomiting
- 2) CVS: Stimulation ↑ force of contraction, tachycardia – BP
- 3) Smooth Muscle: Relaxation -Most prominent Bronchial -↑ VC
- 4) Kidney: Mild diuretic
- 5) Stomach : ↑ secretions
- 6) Skeletal Muscle: ↑ contractile power
- 7) Mast cells, inflammatory cells: ↓ release of histamine & mediators
- 8) Metabolism: ↑ BMR

# THREE DISTINCT ACTIONS

## a) Inhibition of phosphodiesterase

- ATP    Adenylyl cyclase    cAMP    Phosphodiesterase    5AMP  
or    - GTP    Guanylyl cyclase    cGMP

## Inhibited by Theophylline 5GMP

- accumulation of cyclic nucleotide- ↑ signal

# transduction -

## Bronchodilatation, cardiac stimulation & vasodilatation

## - Inhibition of PDE4 & PDE5

## (PDE4) Bronchodilatation

b) Release of  $\text{Ca}^{++}$  from sarcoplasmic reticulum - skeletal & cardiac. At higher conc. than therapeutic plasma conc.

c) Competitive antagonist at adenosine receptor - Adenosine – contract smooth muscle, dilate cerebral blood vessel, depress cardiac pacemaker, inhibit gastric secretion

# ADVERSE EFFECTS



PHARMACOKINETICS- cross placenta, secret in milk

$T_{1/2}$  – Adult-7-12hrs Children- 3-5hrs premature infant-24-36hrs & with higher doses up to 60 hrs

## INTERACTIONS:-

- 1) Inducer - ↑dose – Phenytoin, Rifampicin, Phenobarbitone
- 2) Inhibit metabolism- ↓dose- Erythromycin, Ciprofloxacin,  
Cimetidine, OC Pills, Allopurinol
- 3) Theophylline ↑ effect of – Furosemide, Digitalis,  
Anticoagulants, Sympathomimetics, Hypoglycemics
- 4) Theophylline - ↓ effect of Phenytoin, Lithium

DOSE:- Theophylline – 100-300mg TDS (15 mg/kg/day)

Aminophylline- 250-500mg slow iv

Doxophylline:- Long acting,

- Not interfere- sleep, G I secretion
- 400mg OD in evening

PDE4 Inhibitors- Cilomilast &

Roflumilast In Asthma Theophyllines :

- Bronchodilatation,
- ↓ release of inflammatory mediators,
- improve mucociliary clearance,
- stimulate respiratory drive &
- ↑ diaphragmatic contractility

# C} ANTICHOLINERGIC AGENTS

Atropinic drugs – block constrictor tone, large airway

## IPRATROPIUM BROMIDE:-

- Muscarinic receptor antagonist
- $M_3$  receptor – Bronchoconstriction
- Block all type of receptors
- Slow and less intense bronchodilatation
- Dose – 20-40  $\mu\text{g}$  6hrly inhalation

## TIOTROPIUM BROMIDE:-

- Slow dissociation from muscarinic receptors
- High affinity
- OD doses



# II) LEUKOTRIEN ANTAGONISTS

● Leukotrien receptor antagonist- Montelukast & Zafirlukast

● 5 Lipoxygenase inhibitor- Zileuton

History- 1930 Kellaway study leukotrien

- 1990s three drugs released

Mechanism of Action-

- Leukotrien receptor antagonist-

Cysteinyl LT –bronchoconstrictor LTC<sub>4</sub>, LTD<sub>4</sub>,  
LTE<sub>4</sub> & LT<sub>1</sub>

Montelukast & Zafirlukast Pranlukast - high affinity competitive -  
antagonist - cys LT<sub>1</sub> Receptor

Leukotrien synthesis inhibitor- 5LOX Inhibited  
arachidonic acid → Leukotrien by  
5LOX Inhibit formation of cys LTs

# PHARMACOKINETICS & METABOLISM

| DRUG        | Bioavail | Metabolism | Zafirlukast        | 90%             | Prot. B |
|-------------|----------|------------|--------------------|-----------------|---------|
|             |          |            | $T_{1/2}$<br>10hrs | CYP2C9          | >99%    |
| Montelukast | 60-70%   | 3-6hrs     | Zileuton           | CYP3A4 & CYP2C9 | 99%     |
| -           | 2.5hrs   |            |                    | CYPs & UDP-GT   | 93%     |

## Adverse Effects:-

- Zafirlukast & Montelukast- Systemic eosinophilia, Vasculitis, Neuropathy.
- Zafirlukast - warfarin  $\uparrow$ PT
- Zileuton-  $\uparrow$ Liver Enzymes,  $\uparrow$ plasma conc. Theophylline & warfarin

DOSE:- Montelukast- 10 mg OD Children 5 mg OD

Zafirlukast- 20 mg BD Children 10 mg BD

## III) MAST CELL

### STABILIZERS

#### 1) SODIUM CROMOGLYCATE ( Cromolyn Sod.):-

- Synthesized-1965 , plant *Amni visnaga* ,
- use asthma 1973

Mechanism of

Action:-

- Inhibit degranulation of mast cells and other inflammatory cells. Inhibit chemotaxis
- ↓Bronchial hyperreactivity

Pharmacokinetics-

- not absorbed orally
- Inhalation Fraction absorbed excreted unchanged in urine & bile
- $T_{1/2}$  – 45-100min

Adverse Effects- bronchospasm, cough, Throat irritation,  
Laryngeal edema, Headache, Bad  
taste Dose- 1 mg 4 times daily

## 2) NEDOCROMIL:-

1992 , similar to Cromolyn Sod. More effective  
approved  $\rightarrow$  12 yrs

Dose - 4 mg qid

## 3) KETOTIFEN :-

Antihistaminic H<sub>1</sub> with cromoglycate like  
action Realease of mediator inhibited

orally absorbed Bioavai. 50%  $T_{1/2}$  – 22hrs

Adverse Effects:- Sedation, dry mouth, dizziness, wt gain

Dose: 1-2 mg BD Children 0.5 mg BD

## IV)

### CORTICOSTEROIDS

Inhaled  $\beta_2$  agonist for 4 or more times wkly - start inhaled glucocorticoids

Mechanism of Action in

Asthma:- inhibit airway inflammation

Anti-inflammatory effect-

- \*Modulation of cytokine chemokine production,
- \*Inhibition of accumulation of inflammatory cells
- \*Inhibition of eicosanoid production, in Lung tissue &
- \*↓ Vascular permeability
- ↓ bronchial hyperreactivity, mucosal edema & suppress inflammatory response by AG:AB reaction

# INHALED STEROIDS

High topical & Low systemic activity

- 1) Beclomethasone dipropionate
- 2) Flunisolide
- 3) Fluticasone propionate
- 4) Budesonide
- 5) Triamcinolone acetonide
- 6) Mometasone

Newer  
steroids-

- a) on site activated – Ciclesonide, Rofleponide
- b) Soft steroids – improved local topical selectivity  
Lactone GCS conjugate,  
Loteprednol etabonate



Fluticasone Budesonide – higher affinity

- Dose- 100-200  $\mu\text{g}$  BD upto 400  $\mu\text{g}$  QID

Compliance- highly potent Fluticasone,

- Budesonide-BD/OD improve pt compliance

BUDESONIDE - High topical:systemic activity

- Dose – 200-400  $\mu\text{g}$  BD-QiD inhalation

FLUTICASONE PROPIONATE- High potent long acting

- Dose- 100-250  $\mu\text{g}$  OD (max. 1000  $\mu\text{g}/\text{day}$ )

FLUNISOLIDE - 25  $\mu\text{g}$  TDS



## CICLESONIDE-

- Improved topical: Systemic activity ratio
- Prodrug
- esterases in bronchial epithelium
- oral bioavailability <1% Extensively bind to plasma protein
- Dose- 80-160  $\mu\text{gOD}$  in evening inhalation

## SYSTEMIC THERAPY-

Use – Chronic sever asthma & Acute asthma exacerbation.

- Prednisolone 20-60 mg/day (1-2mg/kg) Taper & start inhalation
- Acute asthma exacerbation- iv steroid then shift to oral & taper

# ADVERSE EFFECTS OF INHALED STEROID

- Horseness of voice, dysphonia, sore throat & Oropharyngeal candidiasis- minimized by spacer, gargling & topical nystatin /clotrimazole
- Hypothalamic adrenal suppression-no risk ↑ with  $>1500\mu\text{g}$
- Osteoporosis- female  $500\mu\text{g/day}$
- CHO & Lipid metabolism -  $>1000\mu\text{g/day}$
- Cataract –
- Skin thinning- dose related  $400\text{-}2000\mu\text{g/day}$  purpura
- Growth retardation- no significant risk

# STEROID RESISTANT ASTHMA

Definition- It is defined as a failure to respond to high doses of oral glucocorticoids  
(2wk course of 40mg prednisolone/day)

Two types :-

- Type I:- 90% ↓binding affinity of GCS to T cell receptor
- Type II:- primary inactivity of steroid receptor / abnormally low no. of GCS receptor binding sites



# MANAGEMENT OF STEROID

## RESISTANT ASTHMA :-

- 1) Methotrexate: Inhibit amidophosphoribosyltransferase-  
inhibit T cell proliferation, ↓dose ↑sensitivity to  
prednisolone
- 2) Cyclosporin: inhibit T cell proliferation, IL2 & other  
cytokine production
- 3) Leflunomide: DMARDs Th cytokine  
expression suppress
- 4) Rapamycin: inhibit T cell proliferation, cytokine synth
- 5) IV Immunoglobulin: Steroid sparing, costly
- 6) Gold: ↓ steroid use

# V) ANTI IgE ANTIBODY OMALIZUMAB

1921 Prausnitz & Kustner -reagin transfer allergic reaction  
1971 Ishizaka -IgE

Omalizumab – DNA derived humanized monoclonal antibody of IgG1k subclass.  
culture (Chinese hamster ovary cells)

Mechanism of

Action:- Fc-IgE

$\leftrightarrow$  FcεRI

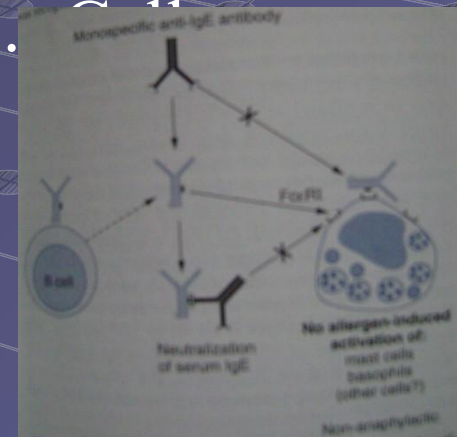
● AG  $\leftrightarrow$  IgE  $\leftrightarrow$  FcεRI → activate mast cell.

● → LTC<sub>4</sub>, PGD<sub>2</sub>, cytokines

● Omalizumab- IgG AB – AG is Fc-IgE (Anti- AB AB)

● Omalizumab + Free IgE → Omalizumab – IgE

Complex, complex, no affinity to FcεRI



# OMALIZUMAB.....

Pharmacokinetics- Single s.c. inj. every 2-4 wks

- Bioavail- 60%,
- $T_{1/2}$ - 26 days

Adverse Effects- well tolerated

- Inj. Site reaction- redness, stinging, induration
- Anaphylaxis 0.1%

In Asthma- >12yrs allergy & mod to severe Asthma

- ↓ exacerbations & steroid req

## PAF ANTAGONIST-

- Ginggolide & structural analogue of PAF
- PAF – bronchoconstriction & edema

# GUIDELINE FOR TREATMENT OF ASTHMA

## 1) MILD EPISODIC ASTHMA –

- ◆ Symptoms < 1 daily & Normal between attacks
- ◆ STEP 1:- Inhaled short acting  $\beta_2$  agonist - onset of attack. No prophylactic t/t.

## 2) MILD CHRONIC ASTHMA –

- ◆ Symptoms once daily or so
- ◆ STEP 2:- Regular inhaled low dose steroids & episode t/t with Inhaled short acting  $\beta_2$  agonist

### 3) MODERATE ASTHMA (Frequent exacerbations)

- ◆ Symptoms >1/day, attack affect activity & sleep
- ◆ STEP 3:- ↑ dose of inhaled steroids (upto 800μg/day)  
+ Inhaled long acting  $\beta$ 2 agonist  
(alternative leukotrien antagonist, Theophylline)  
episode t/t with Inhaled short acting  $\beta$ 2 agonist

## 4) SEVERE ASTHMA -

- ◆ Continuous symptoms Limitation of activity . Frequent exacerbations/Hospitalisation
- ◆ STEP 4:- Regular inhaled High dose steroids (800-2000 $\mu$ g/day) large vol spacer + Inhaled long acting $\beta$ 2 agonist twice daily
  - Additional t/t with 1 or more -
    - i) Leukotrien antagonist/ SR theophylline/ Oral  $\beta$ 2 agonist / Inhaled ipratropium bromide
    - ii) episode t/t with Inhaled short acting  $\beta$ 2 agonist
- ◆ STEP 5:- pt not adequately controlled or needing frequent emergency care

# STATUS ASTHMATICUS (Severe Acute Asthma)

Acute asthmatic attack not responding to routine t/t &  $\beta$ 2 agonist    life threatening

Precipitated by

- i) Acute respiratory infection
- ii) Abrupt cessation of steroid therapy
- iii) Pharmacological stimuli/Allergens
- iv) Acute emotional stress

# MANAGEMENT OF STATUS ASTHMATICUS

1. Hydrocortisone hemisuccinate 100mg iv stat  
f/b 100-200mg 4-8hrly infusion ( take 6hrs to act)
2. Nebulized Salbutamol (2.5-5mg) + Ipratropium  
bromide (0.5mg)
3. High flow humidified O<sub>2</sub>
4. Salbutamol /Terbutaline 0.4mg s.c.
5. Intubation & mechanical ventilation
6. Antibiotics
7. Saline + Sod. Bicarbonate  
Aminophylline 250-500mg dil in 20-30ml  
5% Glucose iv over 20-30min

**THANK YOU**