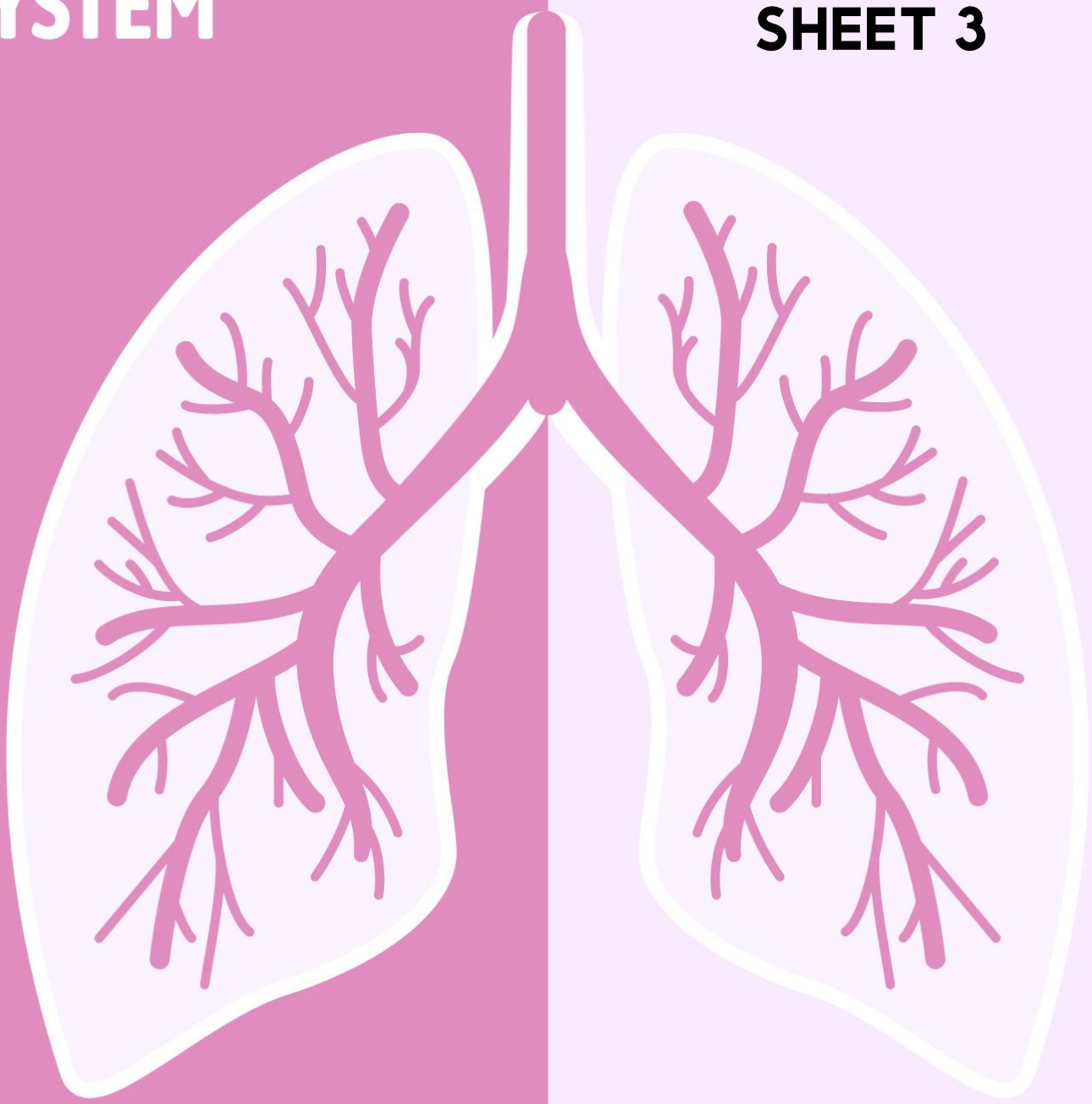
RESPIRATORY SYSTEM

PHARMACOLOGY

SHEET 3



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SHEET 3
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Treatment of Bronchial Asthma

Recall that Medications are divided into 2 main categories:

Categories	Medications
Quick relief medications	1) Inhaled Short acting Beta-2 Agonists 2) Inhaled Anticholinergic 3) Systemic Corticosteroids
Long-term control medications	1) Inhaled Long-acting Beta-2 Agonists (LABA) 2) Topical (inhaled) Corticosteroids 3) Inhaled Cromolyn Na and Nedocromil 4) Oral Methylxanthines (Theophyllines) 5) Oral leukotriene modifiers (LTRA)

Methylxanthines (long term):

➔ Drugs: Xanthine, Theophylline, Aminophylline, Theobromine, Caffeine

Information:	Molecular Actions:	Side effects:
▪ **CNS stimulants** ▪ Cardiovascular stimulants ▪ Oral and intravenous ▪ **Were the mainstay treatment (60s-70s)** ▪ Blood assay is a routine (drug monitoring is required) ▪ Optimal dosing is very difficult ▪ Half-life: 3-16 hours → low therapeutic index	▪ Phosphodiesterase inhibition ▪ Adenosine receptor antagonism ▪ Anti-inflammatory activity - Phosphodiesterase enzyme: it's the enzyme which breaks down cAMP. Recall that cAMP is important for dilatation and relaxation of smooth muscles. - Adenosine causes bronchoconstriction	▪ Cardiovascular stimulants; can cause arrhythmias. ▪ Nausea, GIT irritation, diarrhea ▪ Wide inter-individual variation in the rate of hepatic metabolism ▪ Food and drug interactions (erythromycin and ciprofloxacin)

Note: Use of low dose theophylline, with mean plasma level of 36.6 µmol/ml (6.7 µg/ml), significantly inhibits the Late Asthmatic Reaction (LAR) and airway inflammatory infiltration.

Anticholinergic Agents (short term):

Atropine :

Information:	Side effects:
▪ Can be inhaled, but; can cause systemic side effects	▪ Impairs mucociliary clearance leading to dryness, and consequently, impaired clearance of airway secretions.

Ipratropium Bromide Inhaler :

Information:	Side effects:
▪ Poorly absorbed from respiratory mucosa. ▪ Doesn't impair clearance of airway secretions. ▪ Metered dose inhaled and as a solution for nebulization. ▪ Mainly for COPD, not for asthma, because of slow onset (10-15 minutes) and low potency. **NOT USED FOR EMERGENCY** ▪ Might be very useful in special conditions (beta blocker-induced asthma, resistant attacks, cardiac patients)	▪ Causes minimal cardiac or central effects.

Anti-inflammatory agents and Alternative therapy:

- Corticosteroids
- Inhibitors of Mast Cell Degranulation
- Leukotriene Pathway Modifiers
- Immunomodulatory Agents

Corticosteroids (short & long term):

Information:	Actions:	Side effects:
▪ Inhibits the synthesis and release of chemical mediators (histamine, PGs and cytokines) ▪ Suppress the inflammatory cell influx and process ▪ Relax bronchial smooth muscle ▪ Enhance beta-adrenergic responsiveness (upregulate **β receptors**) ▪ Increase synthesis of adrenergic mediators ▪ Decrease quantity and viscosity of secretions ▪ Inhibit IgE synthesis ▪ Decrease microvascular permeability	➔ Highly lipophilic ▪ Binds to cytosolic receptors ▪ The drug-receptor complex enters the nucleus ▪ Decrease transcription of genes coding for pro inflammatory cytokines ▪ Takes several hours to days to work	**Local side effects:** ▪ Hoarseness of voice (dysphonia) ▪ Sore throat and cough ▪ Candida infection **Systemic side effects:** ▪ Osteoporosis ▪ Cataract ▪ Glaucoma ▪ Growth retardation ▪ Adrenal suppression ▪ CNS effects and behavioural disturbances ▪ Increased susceptibility to infections ▪ Teratogenicity

➔ Short term systemic use in severe refractory attacks.

➔ Long term use for "Steroid Dependent" asthma.

Type	Information	Drugs
Short term corticosteroids	▪ Systemic use ▪ Oral or injectable	▪ Cortisone ▪ Prednisolone ▪ Dexamethasone
Long term corticosteroids	▪ Taken by inhalation ▪ Aerosol treatment is the most effective way to avoid the systemic adverse effects	▪ Beclomethasone ▪ Trimacinolone ▪ Flunisolide ▪ Budensonide ▪ Fluticasone

Cromolyn Na and Nedocromil Na (long term):

*They're inhibitors of Mast Cell degranulation

-> Recall that Ag-Ab reaction occurs on the mast cells, and it causes the breakdown of mast cells releasing Histamine. Histamine is a bronchoconstrictor.

Information:	Actions:	Side effects:
▪ Inhibit the release of inflammatory mediators from mast cells **(Mast Cell stabilizers)** ▪ Prophylactic for mild to moderate asthma ▪ Not for acute asthma ▪ Regular use (4 times daily)	▪ Phosphorylates a cell membrane protein, so, mediators release is inhibited despite antigen-IgE interaction ▪ Might decrease Ca++ ▪ Might decrease neural pathways, plasma exudation and inflammation in general	▪ NO SIDE EFFECTS

Leukotriene Pathway modifiers (long term):

➔ Some information about leukotrienes:

- Leukotrienes are synthesized by mast cells and eosinophils.
- They're 1000-fold more potent than histamine in stimulating airway smooth muscle constriction.
- They also promote microvascular leakage, mucus secretion and eosinophil chemotaxis
- Pathway augmented by COX inhibitors (i.e., NSAIDs)

➔ Some information about leukotriene pathway:

- 3-5% of adults with asthma, have "aspirin sensitivity"
- **This reaction is not an allergic response**, can be induced by many different chemicals (**tetrazine, FDC Color #5**), and does not involve IgE antibody response.
- Patients produce high levels of cysteinyl leukotrienes in response to COX inhibitors, **probably by shunting of arachidonic acid into leukotriene pathway.**
- Abnormality of the promotor region of the gene for LTC4 synthase, leading to overexpression of the enzyme leading to increased conversion of LTA4 to LTC4

➔ Examples on leukotriene pathway modifiers:

Drugs	Information
Zileuton	▪ **Inhibitors of 5- Lipoxygenase enzyme** ▪ **Used for acute and chronic treatment** ▪ **Hepatotoxic** ▪ Used 4 times daily
Montelukast & Zafirlukast	▪ **Antagonists of Cysteinyl Leukotriene Receptors**

➔ Some patients improve, others do not **(Churg-Strauss Syndrome)**

Churg-Strauss Syndrome:

- Rare reaction in newly treated asthmatic patients.
- Severe inflammatory reaction, pulmonary infiltration, neuropathy, skin rash, and cardiomyopathy.
- A common finding is systemic vasculitis with eosinophilic infiltration and granuloma formation.
- Could also be due to unmasking of vasculitis after steroid withdrawal.

Montelukast/Beta agonist study:

➔ Findings:

- Percent of patients needing systemic use of corticosteroids decreased by 39%
- Decreased night time awakening
- Percent of patients having asthma attacks decreased by 37%
- Need for Beta agonists decreased by 21%

Immunomodulating Biotherapeutics:

Example: Omalizumab

Information:	Actions:
▪ It's a humanized monoclonal anti-IgE antibody raised in mice. ▪ Not recognized as foreign by human immune system. ▪ Given as IV or SC injections every 2-4 weeks	▪ Targeted against the portion of IgE that binds to its receptors (FC-R1 and FC-R2 receptors) on mast cells and other inflammatory cells. ▪ IgE-anti-IgE complexes are cleared from the blood without deposition in the kidneys or joints ▪ Monoclonal antibodies directed against cytokines (IL-4, IL-5, and IL-13), antagonists of cell adhesion molecules, protease inhibitors, and immunomodulators aimed at **shifting CD4 lymphocytes from the TH2 to the TH1 phenotype or at selective inhibition of the subset of TH2 lymphocytes directed against particular antigens**

Status Asthmaticus:

- Life threatening exacerbation of asthma symptoms that is unresponsive to standard therapy, preceded by rapid increase in the daily use of bronchodilators.
- Provocative factor usually present.
- Needs aggressive treatment in the hospital

Therapy of Status Asthmaticus:

- Oxygen.
- Inhaled short acting Beta-2 agonists.
- Oral or parenteral corticosteroids.
- Subcutaneous Beta-2 agonists.
- Inhaled Ipratropium bromide maybe effective in some patients.
- Epinephrine by subcutaneous injection

Note: Status Asthmaticus isn't like acute asthma. Acute attack of asthma is usually relieved (or might be relieved with difficulty) and responds very quickly to routine treatment. But if Asthma keeps recurring again and again, this condition is called Status Asthmaticus

General Therapy of Asthma:

- Oxygen
- Hydration: Oral or Intravenous
- Expectorants
- Antimicrobials

Possible Future Therapies:

- There is evidence that asthma may be aggravated or caused by chronic airway infection with **Chlamydia Pneumonia or Mycoplasma Pneumonia**.
  This may explain the report of benefit from treatment with **macrolide antibiotics (erythromycins)** and, **if confirmed, would stimulate the development of new diagnostic methods and antimicrobial therapies**.

- Feeding **Lactobacillus caseii** to infants born to allergic parents reduced the rate of allergic dermatitis at age 2 years, offers reason for hope.

GOAL:

- No patients should die of an asthma attack at any time, any place!
- Aerosol therapy is available with hand held devices that operate on batteries.
- immediate beta-agonist therapy via an “Epi-pen” is readily available.

THE END