



RESPIRATORY PHARMACOLOGY

STUDY BOOKLET

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Bronchial Asthma

Definition

Chronic inflammatory disease characterized by **reversible bronchospasm** with **bronchial hyper reactivity** to different stimuli (triggers) S/S: wheeze, Dyspnea especially expiratory & cough

Types of bronchial asthma

Type II (atopic or allergic)	Non Type II (Non atopic)
More severe with systemic eosinophilia	Less severe without systemic eosinophilia
responsive to corticosteroids	Less responsive to corticosteroids
- Allergic (atopic) Asthma with +ve serum IgE (Type I hypersensitivity) early in childhood. - Exercise induced asthma. - Late onset eosinophilic asthma (older age).	Less severe without systemic eosinophilia

Classification of asthma

Intermittent (controlled Asthma) Infrequent attacks	Persistent (Partially controlled or uncontrolled) Mild, Moderate, Severe
Depends on Number of bronchoconstrictor episodes, Night time symptoms & peak expiratory flow	

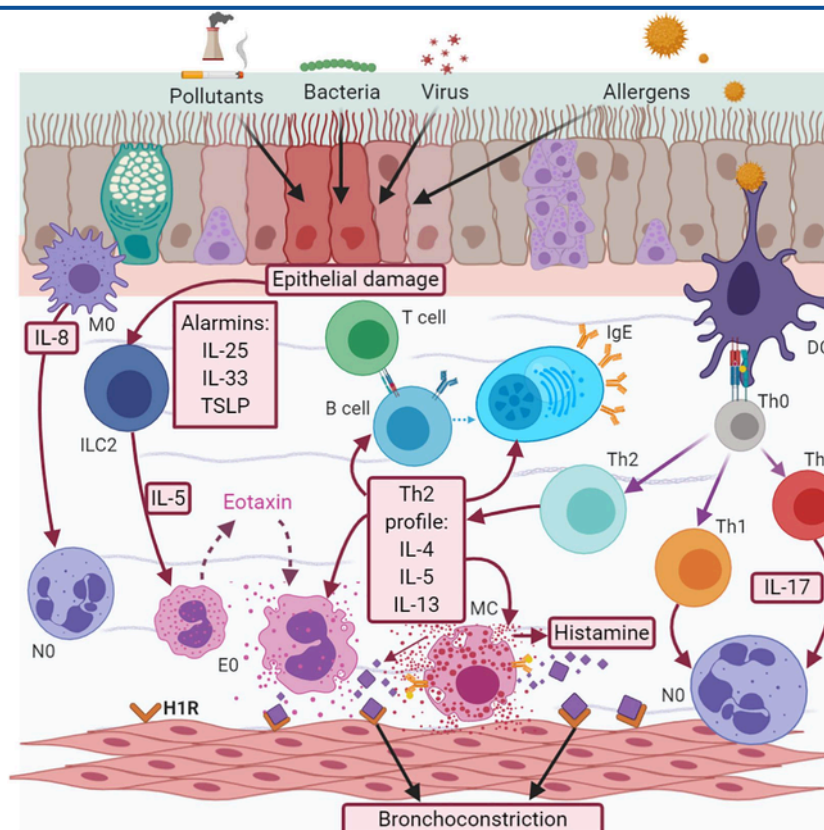
Treatment outline of bronchial asthma

- Pharmacological: Reliever & controller drugs
- Non-pharmacological: smoking cessation, physical activity, Avoid NSAIDs

PATHOGENESIS OF ALLERGIC TYPE II ASTHMA (TYPE I HYPERSENSITIVITY REACTION)

EARLY PHASE: WITHIN 30–60 MINUTES

- 1- Trigger (pollen) is taken by APC.
- 2- **APC** binds to naïve TH cell → **TH2 cell**.
- 3- TH2 cell secretes:
 - * **IL-4** → activate B-cells → changed into plasma cells secreting IgE.
 - * **IL-5** → binds with its receptors on eosinophils → their activation & ↑ survival time.
 - * **IL-13** → ↑ mucous secretion.
- 4- IgE attaches to mast cells (patients become sensitized).
- 5- Subsequent exposure of the trigger → mast cell degranulation → release of stored mediators (mainly histamine & eosinophils chemotactic factors) → Bronchospasm + inflammation.



LATE PHASE: WITHIN 2 TO 7 HOURS

- TH2 cells & Mast cells continue to secrete cytokines (IL-5 & eosinophil chemotactic factor) → continue & intensify the local inflammatory response. (Excess eosinophilia → more tissue damage & ↑ mucous production.)
- Tissue damage → activates arachidonic acid pathway with production of PGs & LTs → bronchospasm, ↑ vascular permeability & chemoattraction for eosinophils.

Drug therapy of Bronchial Asthma

A. SHORT TERM RELIEVERS (BRONCHODILATOR DRUGS)	B. LONG TERM CONTROLLERS (ANTI-INFLAMMATORY DRUGS)
To relieve acute bronchospasm (S/S of acute attack)	To ↓ bronchial hyper-reactivity → ↓ tissue damage & recurrence
1. Short acting β_2 agonists: 1st choice (SABA) 1. Short acting Antimuscarinics 2. Low dose ICS – Formoterol	1. Corticosteroids: Most effective 2. Long Acting β_2 Agonist (LABA) + ICS (not alone) 3. Leukotriene pathway inhibitors 4. cromolyn & nedocromil 5. Anti-IgE: Omalizumab / 3 weeks 6. Anti-IL5: Mepolizumab & Reslizumab 7. Anti-IL5R: Benralizumab 8. Anti-IL4: Dupilumab

N.B

- LABA are the 1st choice (Add-on therapy) to steroids (given in separate or combination inhaler).
- Adding LABA & LT antagonists → ↓ the need to increase corticosteroid dose.
- Short acting theophylline: used as short-term reliever.
- Long acting theophylline (SR): used as anti-inflammatory, especially in patients with COPD.

DRUGS USED IN DIFFERENT TYPES OF ASTHMA

Exercise induced (prophylactic):	β_2 agonists (1st choice) short-term reliever, LT inhibitors.
β blocker & Psychogenic induced: Cardiac, thyrotoxic & old patients:	Antimuscarinic: ipratropium or tiotropium (as bronchodilators).
Aspirin induced:	LTS pathway inhibitors.
Severe uncontrolled allergic asthma:	Omalizumab and other monoclonal antibodies.
COPD:	Tiotropium long acting → useful in maintenance therapy Theophylline: bronchodilator + ↓ diaphragmatic fatigue.
Nocturnal Asthma (dyspnea):	Theophylline → less fluctuation in plasma level and taken once/day.

5 STEP STRATEGY FOR MANAGEMENT OF ASTHMA (ACCORDING TO SEVERITY OF ASTHMA)

As-needed reliever in all steps:

1. **Low dose ICS**
2. **Low dose ICS–formoterol** (as formoterol has rapid onset and relief of symptoms)
3. **Alternative reliever:** Short acting β_2 agonist (SABA)

Step	Preferred controller	Alternative controller
Step 1	As-needed low dose ICS– Formoterol	ICS whenever SABA is taken
Step 2	As-needed low dose ICS–Formoterol	Low dose maintenance ICS
Step 3	Low dose maintenance ICS–Formoterol	Low dose maintenance ICS–LABA
Step 4	Medium dose maintenance ICS–Formoterol	Medium/high dose maintenance ICS–LABA
Step 5	Consider High dose maintenance ICS–Formoterol Add-on: LAMA	Consider High dose maintenance ICS–LABA Add-on: - LAMA - Oral CS (consider side effects)
	+/- (Add-on): Anti-IgE, Anti-IL5/Anti-IL5R, Anti-IL4 (Monoclonal antibodies)	

Step 1: Controlled asthma

Step 2 to Step 5: Partially controlled or uncontrolled

Step 5: Acute severe uncontrolled asthma

N.B

LABA = Long Acting β_2 Agonist

LAMA = Long Acting
Muscarinic Antagonist

ICS = Inhaled
Corticosteroids

- **Cromolyn & nedocromil (rarely used):** May be used in long-term control of mild persistent asthma (with ICS). Never alone.
- **Theophylline** is not recommended by several guidelines, especially in children < 12 years.

A. Bronchodilator Drugs

	1. Adrenoceptor agonists (selective)	2. Antimuscarinic drugs
Mechanism	- Stimulates β_2 receptors $\rightarrow \uparrow$ cAMP $\rightarrow$ - Bronchodilation + $\downarrow$ release of mast cell mediators & cytokines $\uparrow$ bronchial mucociliary clearance - LABA $\rightarrow \uparrow$ anti-inflammatory effect of cortisone ($\uparrow$ nuclear localization of steroid receptor) $\rightarrow \uparrow$ asthma control	Block M_3 receptors in bronchial muscles $\rightarrow$ BD & $\downarrow$ mucous secretion mediated by vagal stimulation - Atropine substitute, Quaternary compound - Taken by inhalation with or without β_2 agonist - Less systemic adverse effect than atropine
Members	SABA: Salbutamol (Albuterol), Terbutaline (all routes) Short (4 hours) / Rapid. Used in children orally. LABA: Formoterol, Salmeterol (inhalation) Longer / slower (lipid soluble $\rightarrow$ dissolve in smooth m. membrane) NB: LABA should be combined with cortisone to avoid $\uparrow$ risk of mortality. (LABA has bronchodilator effect $\gg$ anti-inflammatory effect $\rightarrow$ mask progression of the disease $\rightarrow \uparrow$ risk of mortality)	Short acting: Ipratropium Non-selective $\rightarrow \ominus$ presynaptic $M_2 \rightarrow \uparrow$ release of ACh $\rightarrow$ Tolerance Long acting: Tiotropium Selective M_3 antagonist $\rightarrow$ no tolerance Used as maintenance therapy in COPD (Long acting, No tolerance, Maintenance)
Adverse effects	Tremors (most common), anxiety Tolerance: due to down regulation of β_2 receptors. Tachycardia ($\uparrow$ high concentration $\rightarrow$ stimulate β_1 receptors). Hypokalemia & muscle cramps. Hypoxemia: worsen Ventilation/Perfusion ratio ($V_D > Q_D$) $\rightarrow \downarrow$ blood oxygenation	1. Tolerance: $\ominus$ presynaptic $M_2 \rightarrow \uparrow$ ACh $\rightarrow \downarrow$ effect (unlike Tiotropium) 2. Delayed onset & less effective than β_2 agonist
Indications	Short acting (SABA): As short term reliever: as needed in: - Asthma & COPD - Prophylactic in exercise induced asthma (10 min before exercise) Long acting (LABA): As long term controller in: - Asthma (with corticosteroids) - COPD (maintenance therapy) - Prophylactic in exercise induced asthma 1 hour before exercise	1. Bronchodilator of choice in: Asthma due to psychogenic stimulus or β blockers Asthmatic intolerant to other bronchodilators (esp. thyrotoxic, elderly & cardiac patients) 2. Status asthmaticus (adjuvant to β_2 agonists) 3. COPD (better than in asthma): Tiotropium Since vagal-induced bronchospasm is the only reversible cause of bronchial obstruction in COPD

ORAL LABAs

e.g. SR salbutamol, SR terbutaline & bambuterol (prodrug of terbutaline) may be used as controllers if additional bronchodilation is needed.

Non-selective Adrenoceptor Agonists

Epinephrine (α , β_1 , β_2): Largely replaced by selective β_2 agonists because Epinephrine is:

A. Shorter action

B. Non-selectivity → dangerous tachycardia, arrhythmia (β_1) & hypertension (α_1).

Mainly used in acute attacks of bronchospasm especially in Anaphylaxis

→ rapid β_2 bronchodilation, β_1 cardio stimulant & α_1 vasoconstriction → support blood pressure & decongestant effects).

Ephedrine: Rarely used. Has CNS & addictive adverse effects.

METHYLXANTHINES

Mechanism of action	↓ Phosphodiesterase enzyme (PDE) → ↑ cAMP → - Bronchodilation - Anti-inflammatory: ↓ release of mast cell mediators & cytokines (↓ late asthmatic response) - Block A_2 receptors → Bronchodilation
Pharmacokinetics	Absorption: Xanthine basic & their salts are absorbed from GIT Metabolism: 90% by hepatic cytochrome P450 Elimination: saturation kinetics → ↑ risk of toxicity <i>Many drug interactions</i>

Contraindications of methyl xanthine

- Peptic ulcer
- ISHD
- Epilepsy

**FACTORS AFFECTING THEOPHYLLINE CLEARANCE
REQUIRING DOSE ADJUSTMENT**

↑ $T_{1/2}$ & SERUM LEVEL → ↓ DOSE	↓ $T_{1/2}$ & SERUM LEVEL → ↑ DOSE
Neonates & elderly (extreme of age) Hepatic & heart diseases Viral infections Enzyme inducers: Erythromycin- oral contraceptives Ciprofloxacin -zileuton-zafirlukast.	Children Heavy smokers Heavy drinkers Enzyme inducers: Rifampicin, Phenobarbitone, Phenytoin, Carbamazepine

ACTIONS- ADVERSE EFFECTS & PRECAUTIONS OF THEOPHYLLINE

PHARMACOLOGICAL ACTIONS	ADVERSE EFFECTS - PRECAUTIONS
Anti-asthmatic effect Bronchodilation → relieve acute bronchospasm Anti-inflammatory (Modest) → control chronic asthma	
CNS Alertness – insomnia – nervousness. Tremors – convulsions (high dose). Respiratory stimulant.	Headache. Insomnia – Anxiety. Convulsions. – epilepsy
CVS +ve inotropic & chronotropic VD (except cerebral BV) in high doses → hypotension VC of cerebral blood vessels.	Sinus Tachycardia & arrhythmias. – ISHD Cardiac arrest if given rapidly → given slowly IV. Hypotension.
GIT: Stimulatory ↑ HCl & gastric irritation	Anorexia- nausea , vomiting (give with meals; CI peptic ulcer). Proctitis (suppositories).
Skeletal muscle ↑ contractility & reverse fatigue of diaphragm in COPD → ↓ dyspnea	
Kidney weak diuretic action.	
High Risk of toxicity: Narrow safety margin & saturation kinetics.	Monitor serum level – adjust dose (see kinetics).

Preparations	- Aminophylline: High solubility → given by many routes: oral, rectal & slowly IV - SR theophylline: less fluctuation of plasma level → effective as control medication & in nocturnal asthma - Low dose theophylline: Provide full anti-inflammatory effect. Less side effect & no need to monitor its plasma level
Indications	BA (2nd or 3rd choice): Short term relief of acute asthma Long term control esp. nocturnal asthma (SR theophylline) Acute severe asthma COPD (bronchodilator & reverses diaphragmatic fatigue) Respiratory stimulant in neonatal apnea (caffeine)
Advantages	- Cheap - Can be given by many routes (except inhalation)
Disadvantages	- Saturation kinetics requiring drug monitoring - Narrow safety margin ↑ Risk of drug interactions

ANTI-INFLAMMATORY DRUGS

	Glucocorticoids	Leukotrienes Pathway Inhibitors	Cromolyn & Nedocromil
Mechanism	Immunosuppressive & anti-inflammatory ⊖ PLA₂ & cytokines → ⊖ mediators release & reflux of inflammatory cells → ↓ inflammation & hyperreactivity → ↓ recurrence of attacks Potentiate β₂ agonists: ↓ tolerance to β₂ agonists by ↓ down-regulation of receptors	- Zileuton: ⊖ 5-lipoxygenase (LOX) → ↓ LT's synthesis. - Not commonly used due to hepatic toxicity. - Zafirlukast & Montelukast: LTS receptor antagonists → bronchodilation + anti-inflammatory effect	Weak anti-inflammatory ⊖ Mast cell degranulation → ↓ release of mediators (early response) ⊖ Eosinophil activation → ↓ late inflammatory response to antigen
Indications	control medication - ICS: All steps of persistent asthma (start by small doses & ↑ gradually) - Oral: added to ICS in severe cases Rescue medication (oral: for 7 days max) in acute exacerbation not responding to β₂ agonists - Status asthmaticus (acute severe asthma): Oral or IV ICS + Formoterol: in acute attack as needed	Control medication Alternative to ICS in mild persistent asthma (intolerant to steroid or inhaler) Add-on to ICS in moderate or severe persistent asthma 1st choice in aspirin-induced asthma Prophylactic in exercise-induced asthma	Prophylactic: Inhalation ⊖ Antigenic & exercise-induced asthma (unavoidable) Chronic use: (4 doses/day) in mild persistent asthma (+ICS) → ↓ recurrence (NOT IN ACUTE ATTACK) Allergic rhinoconjunctivitis (drops)
Adverse effects	inhaled CS: Avoided by gargling & spitting after inhalation Use Spacer device Oropharyngeal candidiasis Hoarseness of voice Systemic CS adverse effects: (see box below)	Well tolerated Headache Dyspepsia Zafirlukast: Enzyme inhibitor → drug interaction Zafirlukast & Zileuton → ↑ liver enzyme	Throat irritation, cough & bronchospasm (powder form: avoid by prior inhalation of β₂ agonists) Stinging in the eye

Systemic adverse effects of corticosteroids

- Osteoporosis
- Growth retardation
- Diabetes Mellitus
- Adrenal suppression
- Cataract, glaucoma
- Hypertension
- Cushing syndrome
- Hypokalemia

Others	Inhalation preparations: • Beclomethasone • Fluticasone • Mometasone • Budesonide Ciclesonide: Prodrug activated by bronchial esterases High FPM & high plasma protein binding → less systemic side effects Less frequent candidiasis Oral: Prednisone, Prednisolone Parenteral: Methyl prednisolone, Hydrocortisone	Advantages of LTs pathway inhibitors 1. Oral therapy (easier than inhalation, especially in children) 2. Long duration of action 3. Minimal side effects (well tolerated)	Ketotifen (related to Cromolyn) Mast cell stabilizer Antihistamines
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Monoclonal Antibody (...Mab) Drugs

1. Omalizumab

- **Mechanism:** Humanized monoclonal antibody. Binds to circulating IgE → inhibits its binding to mast cells.
- **Uses:** Add-on therapy in severe uncontrolled allergic asthma (excess serum IgE) → ↓ frequency & severity of exacerbation.
- **Adverse effects:** ↑ risk of anaphylaxis and reaction at the site of injection.

2. Mepolizumab & Reslizumab

- **Mechanism:** Anti-IL-5
- **Uses:** Add-on therapy in severe uncontrolled allergic asthma (not controlled by high dose ICS/LABA)
- **Adverse effects:** Headache & reaction at site of injection

3. Benralizumab

- **Mechanism:** Binds with Anti-IL-5R
- **Uses & adverse effects:** same as (2)

4. Dupilumab

- **Mechanism:** Anti-IL-4
- **Uses:** same as (2) + atopic dermatitis
- **Adverse effects:** same as (2) + blood eosinophilia

1. Mild or Moderate Acute Exacerbation	• Short acting β_2 agonist (SABA) by inhalation. Salbutamol can be given IV. • Oral Prednisone: 40–50 mg • Oxygen (95%)
2. Severe Acute Asthma (Status Asthmaticus)	• Refractory to the usual treatment due to down regulation of β receptors, mucus plug and acidosis • Precipitated by infection, emotion, or allergy • It is an emergency condition requiring hospitalization A. Hospitalization • Endotracheal intubation and suction of secretion • Humidified oxygen inhalation • IV fluids: for correction of dehydration, electrolytes & acidosis • Antibiotics for infections B. Drug Therapy • (Avoid sedatives → Respiratory depression) • SABA: e.g. Salbutamol (inhalation) $\pm$ Ipratropium (inhalation) • Systemic glucocorticoids: • Oral Prednisone: for 7 days (if the patient can swallow) • IV Methylprednisolone (switch to oral when possible) • Aminophylline IV infusion in severe cases (slowly to avoid cardiac arrest) • Artificial respiration

Drug Therapy of Cough

- It occurs due to stimulation of irritant cough receptors in respiratory passages or outside (esophagus, heart or ears).
- Cough reflex is controlled by cough center in the medulla.

Treatment of cough:

Specific Treatment	Non specific treatment
• Bronchodilators β_2 agonists (Salbutamol, Terbutaline) Theophylline • Decongestants (vasoconstrictors) Ephedrine Pseudoephedrine Phenylephrine	If persist & → Insomnia... Or during eye surgery → • Dry cough → Antitussive (Cough suppressants) • Productive cough → Mucolytic Expectorants

Central Antitussives	• Act on cough center in medulla • Used in moderate to severe dry cough A. Opioid Antitussives • Codeine • Pholcodine • Dextromethorphan B. Antihistamines • Diphenhydramine • Carbinoxamine (↓ adverse effect)
Peripheral Antitussives	For mild to moderate dry cough, e.g. sore throat Volatile oil (Menthol) • Mechanism: Demulcent → Protect irritant receptors by layer of mucin (used as lozenges or in hot steam) • Adverse effect: Seizure, coma, death (serious)

Central Antitussives

A. Opioid Antitussives	1. Codeine (Moderate analgesic + Strong Antitussive) Adverse effects: • Drowsiness in adults but paradoxical excitement in children • Mild dependence in abuse • Constipation (chronic use) • Respiratory depression (in large analgesic doses) 2. Pholcodine • Mechanism: Direct depression of cough center in the medulla → suppress cough reflex • Semisynthetic opioid with less adverse effects than codeine (replace codeine) • Adverse effect: Sputum retention 3. Dextromethorphan (1st choice) • Mechanism: Cross BBB → σ_1 opioid receptor agonist & NMDA receptor antagonist on cough center → suppress cough reflex • Adverse effects: Hallucination (serious) • Preferred to codeine: Less liability to constipation, respiratory depression, and dependence than codeine (in antitussive doses)
B. Antihistamines	• Members: Diphenhydramine, Carbinoxamine • Mechanism: H_1 receptor antagonist → suppress central cough mechanism and ↑ threshold for afferent cough impulse • Adverse effects: Anticholinergic adverse effects: dryness of secretion, constipation, urine retention, ↑ IOP, ...

Treatment of Productive Cough

① Mucolytics

↓ Viscosity of bronchial secretion

Therapeutic uses of Mucolytics

- Productive cough
- Asthmatic bronchitis
- COPD
- Pulmonary cystic fibrosis
- Bronchiectasis
- Care of tracheostomy tube
- Acetylcysteine: Antidote in paracetamol toxicity

1. Carbocysteine & Acetylcysteine

Mechanism:

- Break disulfide bonds of thick mucus
- Antioxidant
- Anti-inflammatory

Adverse effect:

Angioedema, Pruritus & peripheral edema

2. Ambroxol

- **Mechanism:** Breakdown acid mucopolysaccharide fibers → make sputum less viscous and easy to expectorate → promote clearance
- **Adverse effect:** Difficulty in breathing and allergic reaction

3. Bromhexine

- **Mechanism:** Same as Ambroxol
- **Adverse effect:** GIT upset (pain in the upper part of the stomach)

② Expectorants

(Used in productive cough)

1. Guaifenesin

- **Mechanism:** ↑ Volume & ↓ Viscosity of bronchial secretion → allow ciliary movement to carry secretion upwards
- **Adverse effects:** Dizziness, Drowsiness, Headache & stomach pain

2. Menthol

- **Mechanism:** Aromatic substance opens airway to help reduce cough and congestion
- **Adverse effect:** Seizure, coma, death (serious)

③ Bronchodilators: (Discussed before)

④ Decongestants: (Discussed before)

COUGH THERAPY CONTRAINDICATED IN CHILDREN

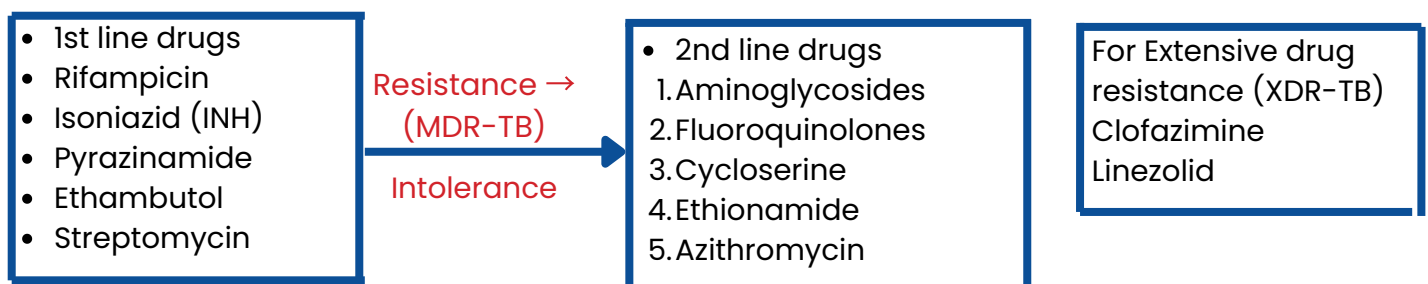
- Dextromethorphan & Pholcodine
- Antihistamines: Diphenhydramine, Doxylamine, Promethazine...
- Guaifenesin
- Pseudoephedrine & Phenylephrine

Drug Therapy of Pulmonary Tuberculosis

Problems with TB

1. **Resistance occurs in monotherapy** → combination therapy is required
2. **Slowly growing organisms** → Treatment should extend up to 2 years to avoid relapse
3. **Poor compliance due to multidrug therapy for long time** → Use direct observation therapy (DOT) to ensure completion of therapy

Antituberculosis Drugs



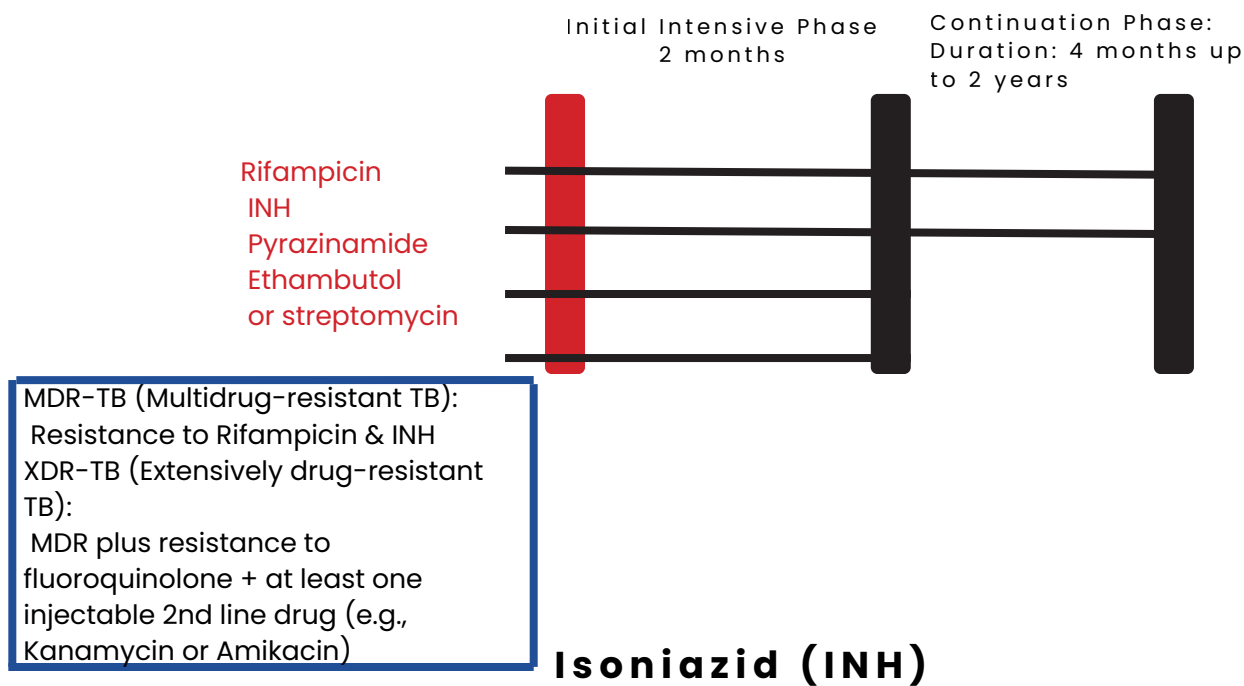
General principles for treatment of TB

1. Bactericidal drugs are preferred.
2. Patient with Latent TB infection (LTBI): can be treated with
 - a. Monotherapy isoniazid (INH) for 9 months.
 - b. Combination of INH and rifapentine for 3 months.

Treatment involves 2 phases:

- A. Initial intensive phase: For 2 months
4 drugs are used to ↓ the number of bacilli to avoid resistance.
Rifampicin + INH + pyrazinamide + ethambutol (or streptomycin).
- B. Continuation phase: For 4 months
2 drugs are used: INH & rifampicin.

- Once susceptibility data are available, the drug regimen can be adjusted & continued for 6 months at least.
- MDR-TB, extra pulmonary TB, TB coinfection with HIV: Need treatment for about 2 years.
- Patient monitoring:
Clinical evaluation & Culture (monthly)
Watching for drug side effects (especially liver).



Mechanism of action: (intracellular & extracellular)

Affects the enzyme responsible for synthesis of mycolic acid in the mycobacterial cell wall → disruption in the bacterial cell wall.

Resistance

Chromosomal mutations → overexpression of the target enzyme.
Cross resistance may occur between INH and ethionamide.

Pharmacokinetics

Well absorbed from GIT & widely distributed into all body tissues and fluids (CSF, pleural and ascitic fluids, sputum, saliva, and caseous tissue).

Metabolized in the liver by acetylation, which is genetically determined.

$t_{1/2}$ = 1 hour with rapid acetylators

$t_{1/2}$ = 3 hours with slow acetylators

Adverse effects (INH)

1. Hepatitis (more with rapid acetylator): rare but fatal [risk ↑ with age, alcoholics, and patients taking rifampin].
2. Hypersensitivity reactions: rash, fever.
3. Neurotoxicity (with slow acetylators) → neuritis, memory impairment & convulsions (B6 deficiency). **Add Vit. B6 supplement**
4. Enzyme inhibitor: ↑ phenytoin & carbamazepine serum level.

Note (N.B.):

INH metabolites inhibit pyridoxine phosphokinase, which converts pyridoxine (Vit. B6) to its active form, required for GABA synthesis.

INH overdose + slow acetylator → ↓ pyridoxal-5-phosphate & ↓ GABA → CNS stimulation

II. Rifamycins (rifampin, rifabutin, rifapentine)

1. Rifampin

Mechanism of action:

Inhibits DNA-dependent RNA polymerase → inhibition of RNA synthesis.

Resistance:

Caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

Antimicrobial spectrum (Broad spectrum / Cidal):

- Effective against mycobacterial tuberculosis (intracellular, extracellular, & in caseous material).
- Effective against Non-tuberculous Mycobacteria (NTM) such as *M. avium*, *M. kansasii*.
- Effective against many gram-positive, gram-negative organisms & *M. leprae*.
- Antiviral effect.

Pharmacokinetics (lipophilic):

- Well absorbed after oral administration.
- Widely distributed in body tissues & fluids (TB cavities, sputum, macrophages killing slowly growing TB bacilli).
- Crosses BBB. Metabolized in the liver & is a potent enzyme inducer.
- Excreted mainly in bile (enterohepatic recycling) & slightly in urine.

Adverse effects (generally well tolerated):

- Skin rash, fever, and GIT upset (most common).
- Liver damage and jaundice (rare).
- Enzyme induction (serious drug interactions).
- Flu-like syndrome (malaise, headache, fever...).
- Red discoloration of urine, tears, sputum, and soft contact lenses.
- Resistance: rapid (but no cross-resistance with other anti-TB drugs).

2.Rifabutin: Preferred in TB patients with HIV. Less enzyme induction → less drug interactions.

3.Rifapentine: Longer half-life → once weekly (better compliance) + INH in LTBI.

III. Pyrazinamide

Mechanism of action & Pharmacokinetics:

- Targets mycobacterial fatty acid synthase-1 gene → involved in mycolic acid synthesis.
- Bactericidal against resistant intracellular bacilli.
- Given orally.
- Crosses BBB & penetrates CSF → valuable in tuberculous meningitis.
- Resistance develops rapidly.

Adverse effects:

1. Hepatitis
2. Hyperuricemia
3. Arthralgia
4. GIT upset

IV. Ethambutol

Mechanism of action & Pharmacokinetics:

Bacteriostatic; enters active mycobacteria → inhibits RNA synthesis.

Well distributed throughout the body.

Crosses BBB.

Adverse effects:

1. Optic neuritis
2. Red/green color blindness
3. ↓ Visual acuity (high dose & renal dysfunction)
4. ↓ Uric acid excretion

Mega Summary

Anti-Tuberculous Drugs

TB Bacilli: grow slowly → need long-term treatment.
 Found (sites): Intracellular, Extracellular, or in necrotic tissues.
 1st Line Anti-TB Drugs

	Rifampicin	Isoniazid (INH)	Pyrazinamide	Ethambutol
Effect	Cidal, in all sites	Cidal, intra & extracellular	Cidal, intracellular	Static
Mechanism	⊖ DNA-dependent RNA polymerase → ⊖ RNA synthesis	⊖ Mycolic acid synthesis → ⊖ Mycobacterial cell wall synthesis	⊖ Mycobacterial fatty acid synthase-1 gene → ⊖ Mycolic acid synthesis	⊖ RNA synthesis
Kinetics	Lipophilic → enter enterohepatic circulation • Enzyme inducer • Metabolized into red metabolites	• Lipophilic • Enzyme inhibitor • Metabolized in liver by acetylation	• Highly lipophilic → enters CSF • Used in TB meningitis	—
Adverse effects	1. Rash, GIT upset (most common) 2. Red coloration of urine 3. Resistance 4. Flu-like syndrome 5. Enzyme inducer → drug interactions 6. Cholestatic jaundice	1. Rash (hypersensitivity) 2. Neurotoxicity in slow acetylators → Neuritis (peripheral & optic), Convulsions (Add B6 supplement) 3. Enzyme inhibitor → drug interactions 4. Hepatitis (R/F)	1. GIT upset 2. Hyperuricemia → Arthralgia 3. Hepatitis	• Eye: optic neuritis • Red/green color blindness • ↓ Visual acuity

Treatment of Respiratory Tract Infections

Upper respiratory tract infection Pharyngitis (Acute throat infection)

Etiology:

Virus: **most common (e.g. rhinovirus, influenza)**

Bacteria: e.g. Group A β -hemolytic streptococci (GABHS)

- Non beta-lactamase producing & no penicillin resistance
- Indication for antibiotic therapy
- Complications:

Suppurative: peritonsillar abscess, otitis media, sinusitis

Non-suppurative: acute rheumatic fever (takes up to 7 days to occur), acute glomerulonephritis

Antimicrobial Therapy

Duration of therapy: 10 days

1. Penicillin (**1st choice**): effective, narrow spectrum, safe & low cost

Penicillin V: oral (bad taste)

Amoxicillin: better taste & ↓ diarrhea → good for children

Benzathine penicillin: single IM dose 1.2 MU

2. Non-type I penicillin allergy: → 1st generation cephalosporin (e.g. Cephalexin, Cefadroxil)

- ⚠ Do not use 2nd or 3rd generation for 10 days

3. Type I penicillin allergy:

Azithromycin for 5 days (avoid AL & Mg antacids)

OR Clindamycin for 10 days

General Approach to Antibiotic Treatment

- Start immediate antibiotic therapy in severe symptoms, history of rheumatic fever, or epidemic.
- Antimicrobial therapy should be limited to those with clinical features of GABHS pharyngitis. Duration of therapy: up to 10 days to prevent complications.
- Antibiotic therapy ↓ infectious period from 10 days → 2 days.
- Children should be kept home until afebrile and for the first 24 hours after antibiotic treatment is initiated.
- Symptomatic contacts may be treated without cultures.

Otitis Media

Two types:

1. Acute otitis media (AOM) → need antibiotic therapy
2. Otitis media with effusion (OME) → no need for antibiotics

Causative organisms:

1. Viral
 2. *S. pneumoniae* (+ve)
 3. *H. influenzae* (-ve)
- (2 & 3 are penicillin-resistant) → may produce β -lactamase enzyme

Adjunctive Therapy (for pain relief):

1. Without fever & mild: topical anesthetic (e.g. Benzocaine) ⚠ **not for children under 2 years.**
2. With fever: Acetaminophen or Ibuprofen (not preferred in children < 3 months and not > 3 days)
3. Decongestants, antihistamines, topical corticosteroids, and expectorants → not proved effective.

Antibiotic Therapy for AOM

I. Without penicillin allergy:

Not severe:

1. 2nd generation cephalosporins: Cefuroxime
 2. Amoxicillin/clavulanate (high dose) → **drug of choice for 10 days**
- Very effective
 - High middle ear concentration
 - Safe & low cost
 - Good taste for children

Severe:

1. Amoxicillin (high dose)/clavulanate (**1st choice**)
2. Ceftriaxone (3rd gen) IV or IM for 1–3 days (patients with oral problems)

II. Non-type I penicillin allergy:

- **Not severe:** 2nd generation cephalosporins (oral), Cefuroxime for 10 days
- **Severe:** 3rd gen. Ceftriaxone (IM/IV) for 3 days

III. Type I penicillin allergy:

- **Not severe:** Macrolides (e.g. Azithromycin), once daily for 3 days (separate from antacids)
- **Severe:** Clindamycin

Duration of therapy:

- Standard duration: 10 days for oral therapy
- Exceptions:
Azithromycin → **3 days**
Ceftriaxone → **3 days**
- ⚠ Avoid Ceftriaxone in patients under 2 months

Sinusitis

Causative organisms: as in otitis media PLUS anaerobes

I. Non-pharmacological

Humidifiers, vaporizers, saline nasal sprays → moisten nasal canal, impair crusting secretion, promote ciliary function

II. Pharmacological Therapy

① Adjuvant therapy

A. Oral Nasal decongestants: avoided in children <2 years & in patients with **HTN or ISHD**

B. Intranasal decongestants: **for 3 days only** to avoid rebound nasal congestion (in severe cases & in patients >6 years)

C. Analgesics: Paracetamol or Ibuprofen (short time to avoid kidney dysfunction)

D. Antihistamines: ⚠ **Do not use 1st generation** → atropine-like action → thickening of mucous secretion.

2nd generation preferred (chronic sinusitis/allergic type).

Contraindicated in acute bacterial sinusitis.

E. Intranasal Glucocorticoids: recommended, esp. in acute bacterial rhinosinusitis with allergic sinusitis history.

② Antibiotic Therapy

Indication: **Persistent** severe acute bacterial rhinosinusitis with **moderate/severe symptoms >10 days**

Duration: 10–14 days, up to 21 days

Acute Bacterial Rhinosinusitis (ABRS)

In children:

- **1st choice:** Amoxicillin/clavulanate
- High dose → appropriate initial therapy if pneumococcal resistance risk
- **Non-type I penicillin allergy:** 3rd generation cephalosporins (e.g., Cefixime) ± Clindamycin
- **Type I penicillin allergy:** Levofloxacin (⚠ risk of arthropathy)

In adults:

- **1st choice:** same as children (Amoxicillin/clavulanate)
- **Doxycycline** (⚠ contraindicated in children)
- **Non-type I penicillin allergy:** same as children
- **Type I penicillin allergy:** Doxycycline or quinolones (Levofloxacin, Moxifloxacin)

Severe & Hospitalization (children & adults):

Ampicillin/sulbactam (IV)

3rd gen. Cephalosporin (e.g., Ceftriaxone IV)

Levofloxacin (IV or Oral)

Diphtheria

Diphtheria antitoxic serum:

- Neutralizes the toxin before irreversible binding and damage.
- Sensitivity test to horse serum must be done before treatment.
- In allergic patients, hypo-sensitization is done by injecting slowly increasing doses of antitoxin.

Penicillin or Erythromycin:

↓ number of *C. diphtheriae* bacilli in the throat → ↓ toxin production.

Tracheostomy:

Indicated in cases of suffocation.

Contacts:

1. **Antibiotic:** single-dose IM penicillin.
2. **Toxoid vaccine:** if not vaccinated or did not complete vaccination schedule.

Lower Respiratory Tract Infection

Bronchitis

Acute Bronchitis

1. **Antibiotics:** only if persistent fever or respiratory symptoms >4–6 days, or in predisposed patients (elderly, immunocompromised).
2. **Mild analgesic–antipyretic therapy:** acetaminophen or ibuprofen ⚠ Caution with ibuprofen: avoid in patients <6 months, elderly, or with poor renal function.
3. **Oral or inhaled corticosteroid:** for persistent cough >14 days.
4. **Limited benefit** of β_2 -receptor agonists.
5. **Mucolytic agents** not supported.
6. **Antitussives (OTC cough mixtures):** use cautiously if cough is productive.

Chronic Bronchitis

Definition: Productive cough with sputum lasting >3 consecutive months per year for 2 consecutive years, without underlying bronchiectasis or tuberculosis.

Common pathogens:

H. influenzae
M. catarrhalis
S. pneumoniae

Duration of therapy: 5–7 days

Fluoroquinolone therapy = short course (5 days, once daily).

Antibiotic therapy – Indications:

1. Moderate to severe symptoms
2. Presence of risk factors:
 - Old age
 - Cardiac disease
 - Repeated antibiotic therapy
 - Home oxygen use

Antibiotics used:

1. Beta-lactam
2. Doxycycline
3. Azithromycin
4. 2nd & 3rd generation cephalosporins

Bronchitis

β 2-adrenergic nebulizer therapy: for children with tendency for bronchospasm.

Epinephrine (nebulizer): more effective than albuterol (β 2 agonist) in hospitalized patients.

Corticosteroids: no proven therapeutic effects or significant harmful effects.

Ribavirin aerosol: approved only for Respiratory Syncytial Virus (RSV) infection.

It requires:

1. Special equipment (small-particle aerosol generator).
2. Specially trained personnel for administration via oxygen hood.
3. Special care to avoid drug particle deposition and clogging of respiratory tubing & valves in mechanical ventilators.

Ribavirin aerosol (important):

For severely ill patients, chronic lung disease, congenital heart disease, prematurity, and immunodeficiency.

Pneumonia

Classification	Common Bacterial Pathogens
1. Community Acquired Pneumonia (CAP):	1. 1st most common: <i>Streptococcus pneumoniae</i> 2. 2nd most common: <i>Mycoplasma pneumoniae</i> 3. <i>Haemophilus influenzae</i> 4. <i>Moraxella catarrhalis</i> (esp. extremes of age) 5. <i>Legionella</i> , <i>Chlamydia</i> , viruses
2. Aspiration Pneumonia: From oropharyngeal or GIT contents Risk factors: GERD, acid suppressants	Oral: Anaerobes, <i>Streptococcus viridans</i> GIT: Enteric Gram-negative bacilli
3. Hospital Acquired Pneumonia (HAP):	Occurs >48 hours after admission to hospital Early onset: no risk factor for resistant pathogens
4. Ventilator Associated Pneumonia (VAP):	Occurs 48–72 hours after endotracheal intubation Pathogens: <i>S. pneumoniae</i> , MSSA, <i>E. coli</i> , <i>Klebsiella</i> , <i>Mycoplasma</i>
5. Health-care Associated Pneumonia (HCAP): Pneumonia in a patient hospitalized for ≥2 days in past 90 days Receiving outpatient IV therapy within 30 days Attending hospital clinic/dialysis in last 30 days Family member with known MDR pathogens	Late onset: Risk factors for resistant pathogens MRSA <i>Chlamydia</i>
6. Pneumonia in Neutropenic Patient:	Pathogens: <i>Staphylococcus</i> , <i>Pseudomonas</i> , fungal infections

Drug therapy of Pneumonia

- First priority: Evaluate adequacy of respiratory function
- Second priority: Selection of best antimicrobials.
- Patient should be scored for severity of the disease → treated as outpatient, Inpatient (out or in ICU)

CURB-65 recommended by the British Thoracic Society

Each risk factor scores one point, for a maximum score of 5:

- Confusion of new onset
- Blood Urea nitrogen > than 7 mmol/l (19 mg/dL)
- Respiratory rate ≥ 30
- Blood pressure < 90 mmHg systolic or diastolic ≤ 60 mmHg

Age ≥ 65 year

- (Score: 0–1): Treat as an outpatient
- (Score 2): short stay in hospital or watched very closely as an outpatient
- (Score 3–5): Requires hospitalization (inpatient) with consideration of ICU admission

Pneumonia Severity Index (PSI)

General Principle for Antibiotics uses in pneumonia

I. Patient with NO comorbidities (e.g. DM, COPD, CHF, renal failure, cancer) OR previous exposure to antibiotics in the last 3 months (No risk of drug resistance)

Start By Monotherapy:

- Azithromycin
- Doxycycline
- Respiratory fluoroquinolones (Levofloxacin, Moxifloxacin)

II. Patient with Comorbidities with NO Previous exposure to antibiotics in last 3 months

- Start Monotherapy: with more potent drugs as fluoroquinolones OR
- Combination chemotherapy (Oral β lactam + Azithromycin) for typical and atypical organisms

III. Patient with Comorbidities & with Previous exposure to antibiotics in last 3 months

As II but select an antibiotic from different class of previously exposed antibiotics in last 3 months

Duration of antibiotic therapy

Adult outpatient:

7-10 days (duration of azithromycin & levofloxacin is 5 days)

Hospitalized patient

- 1. Negative blood culture: 7-14 days
- 2. Positive blood culture: 14 days from the day blood culture become negative

N.B. Patients discharge from hospital within 5 Days if there no complication

If ORSA is suspected

Add vancomycin or linezolid to any regimen

Daptomycin is **NOT USED** as it is inactivated of pulmonary surfactant

If Pseudomonas is suspected

- Two Antipseudomonal antibiotics should be combined:
 - **IV β lactam** (Ceftazidime, Piperacillin-Tazobactam or Meropenem)
 - + **Fluoroquinolones** (Cipro or levofloxacin)
 - **Aminoglycosides + Azithromycin or fluoroquinolone** (IV)

Convert a patient from IV to oral therapy with signs of clinical stability

- Stable vital signs for 24 hours (Temperature, BP, respiratory rate ...)
- The oxygenation is improved and stable
- Tolerating oral therapy with normal functioning GIT



Pharmacology made clear.



هتلاقي هنا كل الريكوردات والملازم والاسئلة مجاناً
جروب الواتس اب العام بنبعت عليه كل المهم



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