Respiratory System

Questions decipher.

Q) Classify drugs in Bronchial asthma. ✓
Q) Treatment of Status asthmaticus ✓
Q) Ipratropium Bromide.
Q) Bronchodilators.
Q) Inhalational therapy in asthma. +++
Q) Choose appropriate drug & justify
- Salbutamol / salmeterol in acute attack of asthma.
- Montelukast / Salbutamol in acute asthma attack
- Salbut / Sod. cromoglycate in "

Q) D/I of ciprofloxacin & theophylline.
- Rationale of combining Salmeterol with fluticasone

Lumi

① drugs for dry cough - ~~Antitussives~~ ✓
② mucolytics - Bromhexine, ambroxol.
③ Salbutamol - MOA, Kinetics, DI, ADR, use, C/I.
④ theophylline. - ADR,
⑤ LT. antagonists - Montelukast, Zafirlukast.
⑥ mast cell stabilizers - Ketotifen, sodium cromoglycate.
⑦ Inhalational steroids - Budesonide, fluticasone.

Q) MOA, ADR, role of methyl xanthines in Bronchial asthma.
Q) mast cell modulators., mast cell stabilizers.
Q) Citrovorum factor rescue → different chapter ▽
Q) Bromhexine.
Q) uses (2) of sodium cromoglycate.
Q) Antitussives.
Q) Bronchodilators.
Q) Basis of use of Montelukast in B. asthma., MOA, uses.
Q) Centrally acting cough suppressants & their use. - dry cough ✓ prod X.
Q) Omalizumab.
Q) Glucocorticoids in asthma.

Status Asthmaticus.

definition:

Severe, life threatening, refractory acute exacerbation of asthma ~~does not respond~~ ∧ to unresponsive initial ~~treatment with standard~~ bronchodilators therapy

DEFINITION

Severe, life threatening refractory acute exacerbation of asthma that is unresponsive to Initial Broadhodilator therapy.

→ Medical Emergency ! requires Immediate & aggressive intervention.

→ most common trigger: upper respiratory tract infections.

Treatment - flow chart (for Korch bookmark)

+

Treat - Expand - if asked for more marks

TREATMENT - Expand.

① IV CORTICOSTEROIDS.

Hydrocortisone hemisuccinate.

100 mg IV stat

followed by

100 - 200 mg IV infusion 4-8 hourly

[. takes 6 hours to act → ie, start ASAP]

② Bronchodilators via Nebulization.

Salbutamol 2.5 - 5 mg +

Ipratropium bromide 0.5 mg.

↓

Intermittent Inhalations driven by O_2.

[Synergistic β_2 agonist + anticholinergic combo]

3. High flow humidified Oxygen.

Maintain: SpO_2 > 92%.

avoid hyperoxia in chronic CO_2 retainers.

4. Parenteral β_2 agonists.

as inhaled drug may not reach smaller bronchi due to severe narrowing/plugging with secretions.

Salbutamol / terbutaline 0.4mg im/sc.

⑤ Intubation & mechanical ventilation if needed.

⑥ Treat chest infections with intensive antibiotic therapy.

⑦ Correct dehydration & acidosis with Saline + Soda Bicarbonate / lactate infusion.

Rx - flowchart ✓✓

Hydrocortisone hemisuccinate 100 mg. IV stat

followed by 100-200 mg 4-8 hourly IV infusion

may take 6 hours to act.

↓

Nebulised salbutamol 2.5-5 mg + ipratropium Bromide 0.5mg.

Intermittent Inhalation driven by oxygen

↓

high flow humidified oxygen inhalation.

↓

Salbutamol / Terbutaline 0.4mg im/sc may be added since inhaled drug may not reach smaller bronchi due to severe narrowing / plugging with secretions.

↓

Intubation & mechanical ventilation if needed.

↓

Intensive antibiotic therapy for chest infection

↓

Saline + sod. bicarbonate / lactate infusion to correct dehydration and acidosis.

if fore high mark — go to explain

Ipratropium Bromide

SAMA

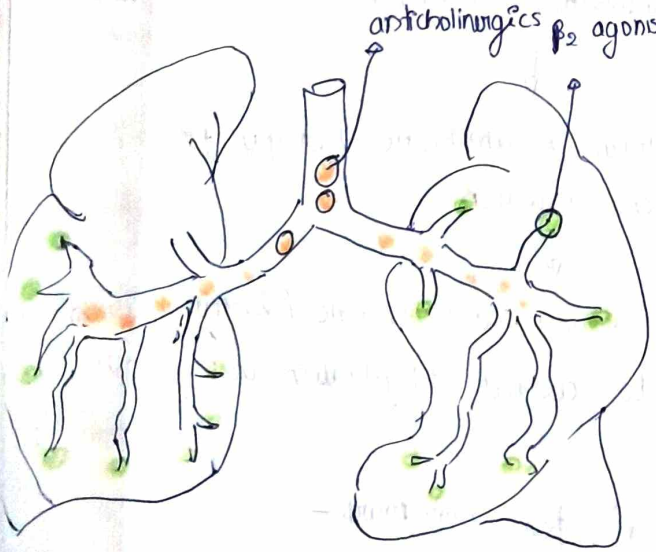
- Ipratropium bromide is a short-acting inhaled, anticholinergic bronchodilator that acts by blocking M_3 receptors, inhibiting vagal-mediated bronchoconstriction, especially in larger airways.

MECHANISM OF ACTION

- Blocks Muscarinic M_3 receptor.
  ↓ cause
  Bronchodilation.

- Blocks cholinergic (vagal) constrictor tone on bronchus.

→ mainly act on larger airways which are richly vagally innervated.



Bronchodilator profile.

SAMA

- type : Short acting M_3 blocker
- Route : Inhalational.
- Onset : Slow (not for acute relief)
- duration : 4-6 hours.
- Metabolism : minimal systemic absorption → fewer s/e.

Clinical uses.

*not for acute monotherapy
*Best for maintenance & prophylaxis
*well tolerated due to low systemic absorption

① less effective in asthma.
- asthmatic bronchitis, psychogenic asthma.
- often combined with β_2-agonists {synergistic action} in refractory asthma.

② DOC in COPD. ☆ reflex cholinergic tone appears to be the major reversible component of airway obstruction
- blocs M_3 receptor in larger airways
- inhibits vagal cholinergic bronchoconstriction
- leads to bronchodilation + ↓ mucous secretions.
- prevents exacerbations.
- tiotropium, glycopyrrolate } is more effective ✓ LAMA.

>24 hours duration

③ COMBINATION of.

Ipratropium + Levosalbutamol.
↓ used in
severe asthma / COPD exacerbations.

PK

- Route : Inhalation. (MDI or nebulizer)
- onset : 15-30 minutes.
- duration : 4-6 hours.
- systemic absorption : minimal → low systemic side effects.
- Excretion : mainly unchanged in urine.

ADR

- dry mouth
- throat irritation.

C/I

- hypersensitivity to atropine.
- narrow angle glaucoma
- prostatic hypertrophy (urinary retention risk).

DI

- synergestic with β_2 agonist
- avoid contact with ocular medications.
  → worsen glaucoma.

Antitussives

- antitussives are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in resp tract to reduce tussal impulse / or both.
- should only be used in dry non-productive cough.

DRUGS FOR DRY COUGH

① Centrally acting Antitussives

- supress cough center in medulla.

- ✓ codeine
- ✓ pholcodine
- ✓ dextromethorphan
- ✓ Noscapine.

② peripherally acting demulcents.

- coat throat mucosa → ↓ irritation.

- glycerin.
- Lozenges.

③ Antihistamines. - for allergic dry cough.

↓ Histamine induce cough reflex.

eg: chlorpheniramine.

NOTE

- Expectorants + mucolytics ✗
  Not in dry cough. ✗
  used in productive cough

- Antitussive
  Should not be used in wet cough → risk of mucous retention.

BRONCHODILATORS

*Relax Bronchial Smooth muscle.

*reverse the Bronchospasm.

Bronchodilators

- Sympathomimetics
- Methylxanthines
- anticholinergics.

β_2 agonist – Most effective Bronchodilator

eg:

- SABA - short acting — Salbutamol, Levosalbutamol
- LABA - long acting. — Salmeterol, Formeterol.
- Ultra - LABA — Indacaterol

MOA

- stimulate β_2 receptors.
- ↑ cAMP.
  - relaxes bronchial smooth muscle
  - ↓ mediator release from mast cells & other inflammatory cells.
  - mucociliary clearance.

ADR

- Tremors
- tachycardia
- T wave change due to
- hypokalemia.
- palpitations.

C/I

- arrhythmia
- hyperthyroidism

USES

- SABA – acute asthma
- LABA - maintenance.
- COPD.

Anticholinergics

		duration
• SAMA	Ipratropium	4-6 hr
• LAMA	Tiotropium, Glycopyrrolate.	≥ 24 hours

MOA

- Block M_3 receptors → ⊖ vagal tone.
- Bronchodilation + ↓ mucous secretions.

USES

- DOC in COPD
- adjunct in asthma.
- bronchitis.

C/I

- BPH
- glaucoma.

METHYLXANTHINES

- theophylline, Aminophylline.

MOA

- ⊖ PDE → ↑ cAMP → Bronchodilation.
- adenosine receptor antagonism ↑ @ therap. con.
- release Ca^{2+} from SR in skeletal & cardiac muscle. at higher plasma conc.

In detail... later.

Q) Choose appropriate drug & justify:

- salbutamol / salmeterol in acute asthma attack.

→ Salbutamol - SABA - for acute attack ✓

→ salmeterol - LABA - slow onset
not for acute relief.

Q) montelukast or salbutamol in acute attack.

- Salbutamol – β_2 agonist → Bronchodilation within minutes.

- montelukast – Leukotriene receptor blocker.
  - slow onset
  - prophylactic only.
  - not for acute attack.

Q) salbu / Sod. chromoglycolate.

Sod. chromo – mast cell stabilizer.
- ↓ no effect on existing attack.
- only in prophylaxis.

Rationale for combining.
Salbu + fluticasone.

dual action

- salbutamol → rapid bronchodilation. (relieves symptoms)
- Fluticasone → reduce airway inflammation.

prevent recurrence.

- asthma is chronic inflammation → causes hyperactive airways.
- ICS ↓ eosinophils, mast cells, cytokines.
  → airway become less sensitive
  → fewer attacks over time.

Enhances β_2 response.

- CS upregulates β_2 receptors.
  ↓
  make salbutamol work better.

MUCOLYTICS

- drugs that breakdown mucous viscosity. making it easier to cough out (used in productive cough)

eg: Ambroxol.
Bromhexine.

MOA

- depolymerize mucopolysaccharides.
  - directly or by liberating lysosomal enzymes.

Ambroxol / Bromhexine.

- Enhances mucous clearance + surfactant production & release.

Uses

- COPD, CF, bronchiectasis.
- post op with retained secretions.

- Bromhexine - adathoda vasica.
- Ambroxol - metabolite of Bromhexine.

ADR

- Rashes.
- Bronchospasm.
- peptic ulcer, gastritis.

C/I

- peptic ulcer
- asthma.
  risk of bronchospasm.

Salbutamol

- selective β_2 - adrenergic agonist.
- SABA - short acting β agonist
- Highly selective β_2 agonist.

MOA

- cardiac side effects are less prominent.
- selectivity increased by Inhalation
  - delivered by pressurized MDI.

MOA

- Stimulate β_2 receptors.

(1) ↑ cAMP formation in Bronchial smooth muscle → relaxation.

(2) ↑ cAMP formation in mast cells and other Inflammatory cells
  - ↓ mediator release.

(3) ↑ mucociliary clearance

PK

- route: Inhalational (preferred) oral, IV, subcutaneous.
- onset: within 5 minutes [inhaled]
- duration: 2-4 hours.
- metabolism: Hepatic
- excretion: renal.

USES — (used to abort & terminate attacks of asthma.)

- DOC in acute Bronchial asthma.
- Exercise-induced asthma.
- ~~COPD~~.
- COPD - symptom relief.

ADR

- Tremors
- Tachycardia, palpitations.
- hypokalemia.
- T-wave changes

C/I

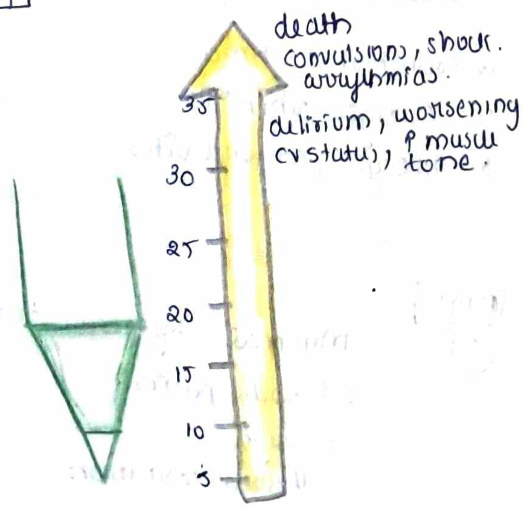
- Cardiac arrhythmias.
- Severe hypertension.

D/I

- diuretics + salbutamol → additive Hypokalemia.

efficacy

Toxicity



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(Diagram in Text) — Study ~~focus~~

alliest

~~No~~ pressure ! (Yes)

METHYL XANTHINES

MOA

① Inhibits phosphodiesterase that degrade cyclic nucleotides intracellularly.

cAMP

theophylline ⊖ | PDE.

↓

5-AMP.

② Blockade of adenosine receptors.

③ release of Ca^{2+} from SR, especially in skeletal & cardiac muscles.

ADR

- theophylline - narrow margin of safety.
- dose-dependent toxicity occurs.
- early symptoms: Headache, nervousness, nausea.

- CNS: insomnia, restlessness, seizures - high dose.

CVS - tachycardia

GI - Nausea, vomiting, acid reflux.

Metabolic - hypokalemia, hyperglycemia.

Leukotriene antagonist

- Montelukast, Zafirlukast.

MOA, Pharmacological basis in asthma use

- block Cys LT_1 receptors.

↓

⊖ effects of cysteinyl leukotrienes.

LTC_4, LTD_4

↓

↓ bronchoconstriction.
↓ mucous secretion
↓ vascular permeability
↓ eosinophil recruitment

USES

- prophylactic therapy of mild to moderate asthma.
- alternative to inhaled glucocorticoids.
- effective in aspirin induced, exercise induced asthma.
- not useful in acute attack of COPD.

mast cell stabilizers.

- sodium cromoglycate.
- Ketotifen

MOA

- Inhibits degranulation of mast cells by trigger stimuli.
- prevents release of asthma mediators like
  - Histamine
  - LT
  - platelet activating factor.
  - Interleukins.
- acts by blocking delayed Cl^- channels
→ prevents calcium influx

↓

No mast cell activation.

- Not a bronchodilator ✗
- ineffective in ongoing attack ✗

USES

- Sodium cromoglycate. - only prophylactic

1. Bronchial asthma.
2. Allergic rhinitis
3. allergic conjunctivitis

ADR

SodC

- Minimal systemic toxicity
- Brochospasm.
- cough
- throat irritation

INHALATIONAL STEROIDS

- Beclomethasone
- Budesonide
- Fluticasone
- Ciclesonide ...

MOA

① Antiinflammatory action : Suppresses Bronchial Inflammation.

↓

- Inhibition of production & release of inflammatory cytokines & mediators:

PGs & LTs → thereby preventing:

✓ smooth muscle contraction
✓ airway mucous secretions

② potentiating effect of β_2 agonist.

INDICATIONS

- all cases of persistent asthma when inhaled β_2 agonists are required almost daily or the disease is not only episodic

- use of SABA > 3times/week
- night time symptoms ≥ 1 /week.

USES

- first-line therapy in all persistent asthma.
- not in acute exacerbation X.
- MART regimen : maintenance and reliever therapy.

Budesonide + Formoterol
(ICS) + (fast acting LABA)

ICS in Combination

- WHO & GINA recommended:

(Budesonide + Formoterol)

ADR

local

- Hoarseness, dysphonia.
- Sore throat.
- Oropharyngeal Candidiasis. : minimized by spacer, gargling.

Systemic @ high doses.

- Mood changes.
- hyperglycemia.
- osteoporosis.
- cataracts, bruising.

Budesonide : intranasal spray for P/O & Rx of seasonal & perennial allergic or vasomoto rhinitis, nasal polyposis.

Beclomethasone : perennial rhinitis.

Systemic corticosteroids

→ Severe chronic asthma.
→ status asthmaticus.
→ COPD.

OMALIZUMAB

→ Humanized monoclonal antibody targeted against IgE.

MOA

It neutralize free IgE in circulation without activating mast cells & other inflammatory cells.

Route : Subcutaneous

USE : resistant asthma patients with positive skin test or raised IgE levels.

Inhalational therapy in asthma

- β_2 agonist
- anticholinergics.
- mast cell stabilizers.
- Glucocorticoids.

aim: to deliver drug to site of action so that lower dose is needed & systemic side effects are minimized.

→ MDI
→ Nebulizers.
→ Dry powder inhalers (DPI).