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Week 1 26/2/2018

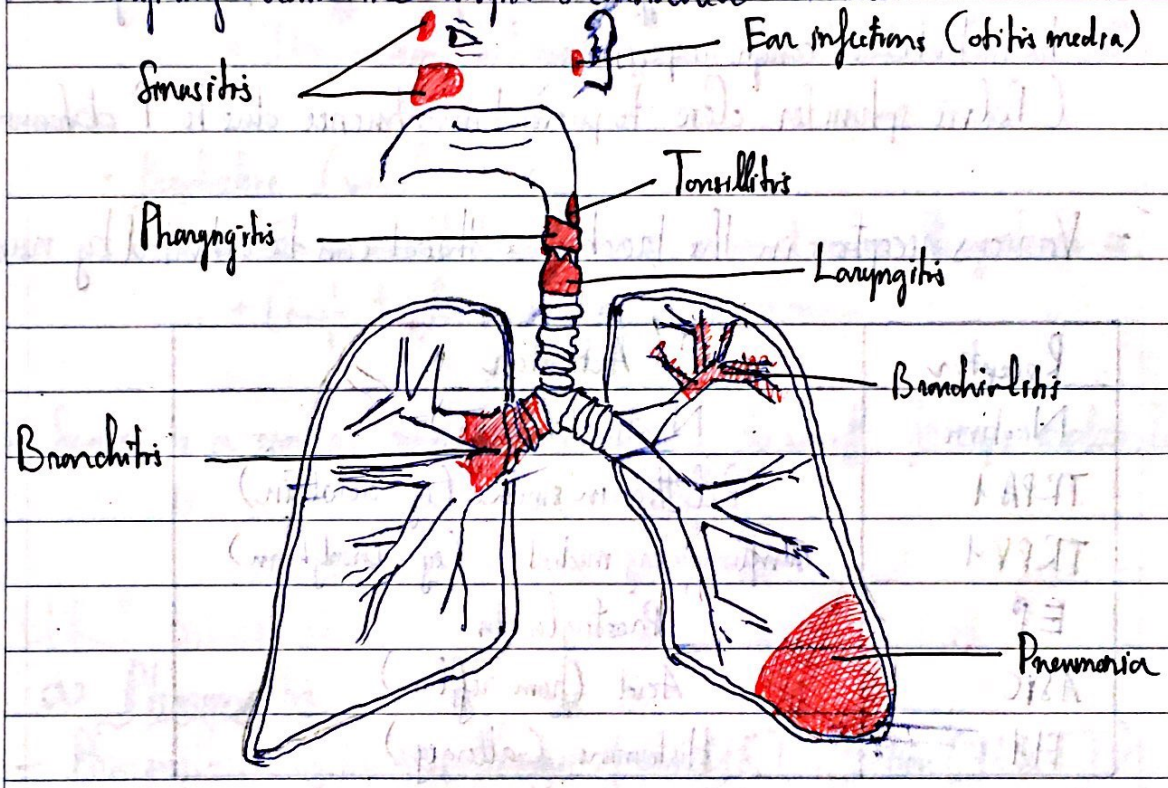
I) Protective mechanisms against URT ailments
Cause / symptoms of cold & flu

Upper respiratory tract (URT) introduction

- Review PHR 1051 week 10

URT consists of the nasal cavity (sinuses), pharynx & larynx

Everything below the larynx is considered "lower"



Protective mechanism of the URT

∿ Mucus

- Mucus is a viscoelastic gel { water, high MW molecules, crosslinked glycoproteins

Mucus also contains > 100 compounds w/ antimicrobial & anti-inflammatory activity

→ Protection in both upper & lower RT by engulfing & removing foreign bodies

→ Rhinitis when getting an URT infection

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Cough

- Acute cough is considered important in removing foreign bodies from the lung, but chronic cough is non-beneficial in general.
- Mucus is cleared from the lung thru coughing, which can be triggered on irritation to the RT, due to allergic reaction, COPD, asthma,...

- Irritants activates receptors on sensory neurons, to the cough center in the medulla, then sends efferent message back to the larynx & the muscle to initiate a cough response.
  (Pelvic sphincter close to prevent incontinence due to ↑ abdominal pressure)

- Various receptors in the trachea & throat can be activated by numerous stimuli:

Receptor	Activator
Nicotinic	Nicotine (smoke)
TRPA1	Pollution in smoke (eg. acrolein)
TRPV1	Inflammatory mediator (eg. bradykinin)
EP	Prostaglandin
ASIC	Acid (from reflux)
H1	Histamine (allergy)

Some receptors in the cough center are responsible for tussive response:

Receptor	Activator	Response
μ-opioid receptors	Enkephalins, antitussives	↓ cough
NMDA receptors	Glutamate	↑ cough

- While acute cough is more relevant to receptors in the UIRT, chronic cough is more associated w/ cough receptors in the nervous system generally.

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- Chronic cough can be caused by various conditions
  Eg: Asthma, COPD, GORD, consistant exposure to irritants, drug side effe

- Both chronic & acute cough can be unproductive or productive
  - Unproductive (dry/hacking):
    + No abnormal production of mucus of LRT
    + Results from pharyngitis or irritation of cough receptors
    + Uneffective & unnecessary.
    + It is common to have dry cough for 1 week after an URT infection

  - Productive (wet/chesty)
    + Excess bronchial secretion & impaired mucociliary clearance
    + Cough to loosen & bring up excess mucus

- Sneezing is a similar mechanism to coughing to expel foreign materials

URT symptoms

∿ Pharyngitis

- Pharyngitis may be the 1st sign of an URT infection (URTI)
  Most often caused by viral infection (eg rhinovirus, influenza)
  → Infected pharynx leads to the classic sore & painful throat (inflammation)

- Infection by streptococcus bacteria is unusual, most likely affect 4-15yo (not <3)
  Commonly termed "strep throat", symptoms included:
  - Sudden, severe sore throat
  - Pain on swallowing
  - Fever > 38.5°C
  - Swollen tonsil & lymph nodes
  - White/yellow spots w/ bright red throat

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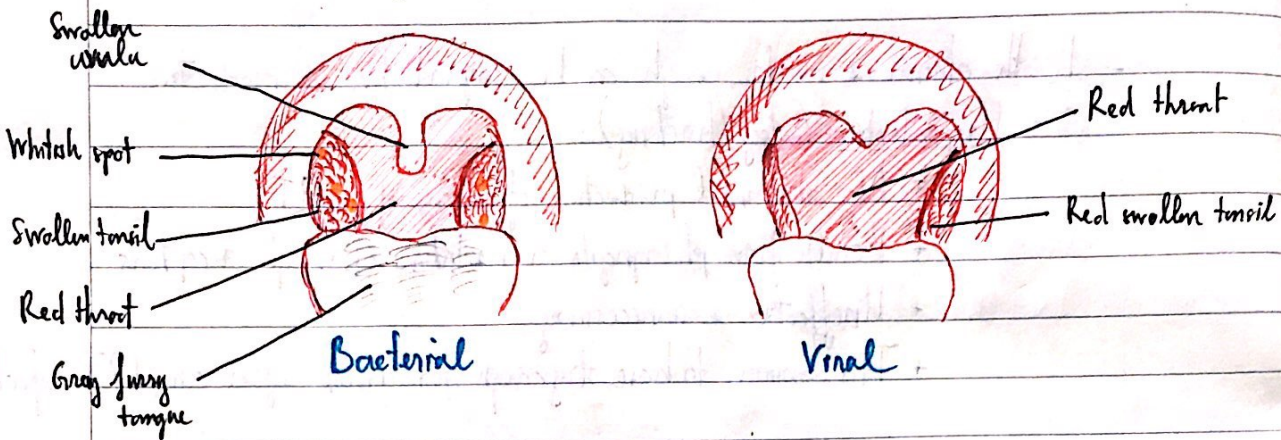
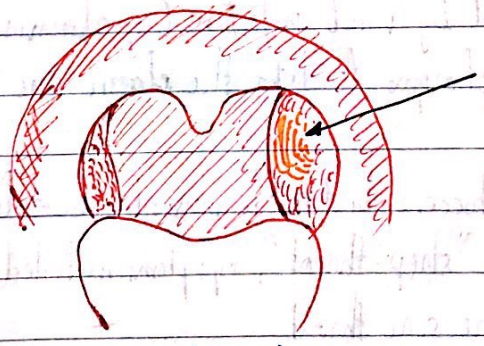
- Viruses & bacteria are transmitted by breathing, coughing or sneezing.
  Symptoms usually appear after 2 - 5 days



∞ Tonsillitis

- One can have pharyngitis & tonsillitis at the same time
  Symptoms, diagnosis & treatment are similar to pharyngitis

- Antibiotics can prevent complications of bacterial tonsillitis
- Tonsillectomy for those (especially children) who have:
  - Recurrent severe tonsillitis
  - Obstructive sleep apnea due to enlarged tonsils or adenoids
  - A peritonsillar abscess (quinsy) centering pus



Peritonsillar abscess

~ Laryngitis

- Laryngitis is inflammation of the larynx & produces symptoms eg. a hoarse voice. This is due to the obstruction of the vocal cords.

Headache, fever & cough may be associate

- These symptoms start suddenly & worsen in 2-3 days, but usually improve within 7 days w/o treatment

- Laryngitis, pharyngitis & tonsillitis are caused by same viruses that cause common cold or influenza
Laryngitis can be caused by shouting alot.

Management of sore throat

- Non-pharm & pharmalogical options:
  - Gargle w/ warm salty water or suck on an icecube
  - Drink hot water w/ lemon & honey (short lasting)
  - Suck on a throat lozenge (some contain NSAIDs)
  - Gargle w/ a sore throat gargle or use throat spray
    + Some gargles contain local analgesic (eg. benzocaine)
    + Others contain povidone-iodine (antibacterial & antiviral)

- Resting is always good, drink plenty of water & non-alcoholic fluids
- For relieving pain & fever, paracetamol, NSAIDs can be recommended.
Antibiotic may not be useful except for 'strep throat' or secondary infection due to immunocompromised conditions

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CARER protocol

- CARER is one of various protocols that can be used to collate info from patients

Later will be introduced to the Monash Model of Care (MMoC), consists of 4 main parts.

- Connect / Collaborate
- Assess / Apply
- Recommend
- Educate / Ensure monitoring & follow up

- Refer to the hand-made APF note in "cough"

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II) Cause / symptoms of flu & cold

The common cold & influenza

Common cold

- Caused by viruses eg. rhinoviruses, coronaviruses, adenoviruses
- Due to various virus types, quick mutation
  → hard to vaccinate against common cold

- Children tends to get common cold more often (5-10/year compared to 2-4/y)

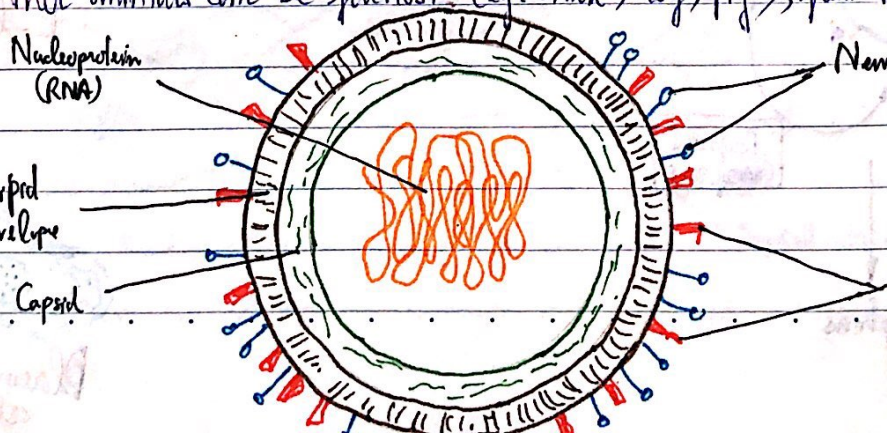
- Antibiotic is useless against viral infection, even a problem due to resistance

Influenza

- Flu is also caused by viruses, either influenza virus A, B or C
  - Most case caused by influenza A
  - Influenza B often associated w/ localized outbreak
  - Influenza C is mostly asymptomatic

- Like common cold, mutation (antigenic shift) leads to different strains of influenza
  → A cell can be infected by 2 different strains of influenza A simultaneously

- Different strains of influenza are numbered according to major surface antigens
  hemagglutinin & neuraminidase
  Eg.: Influenza A w/ hemagglutinin 1 & neuraminidase 1 would be H1N1
- Other animals can be flu host (eg. chick, dog, pigs), from which can spread to human



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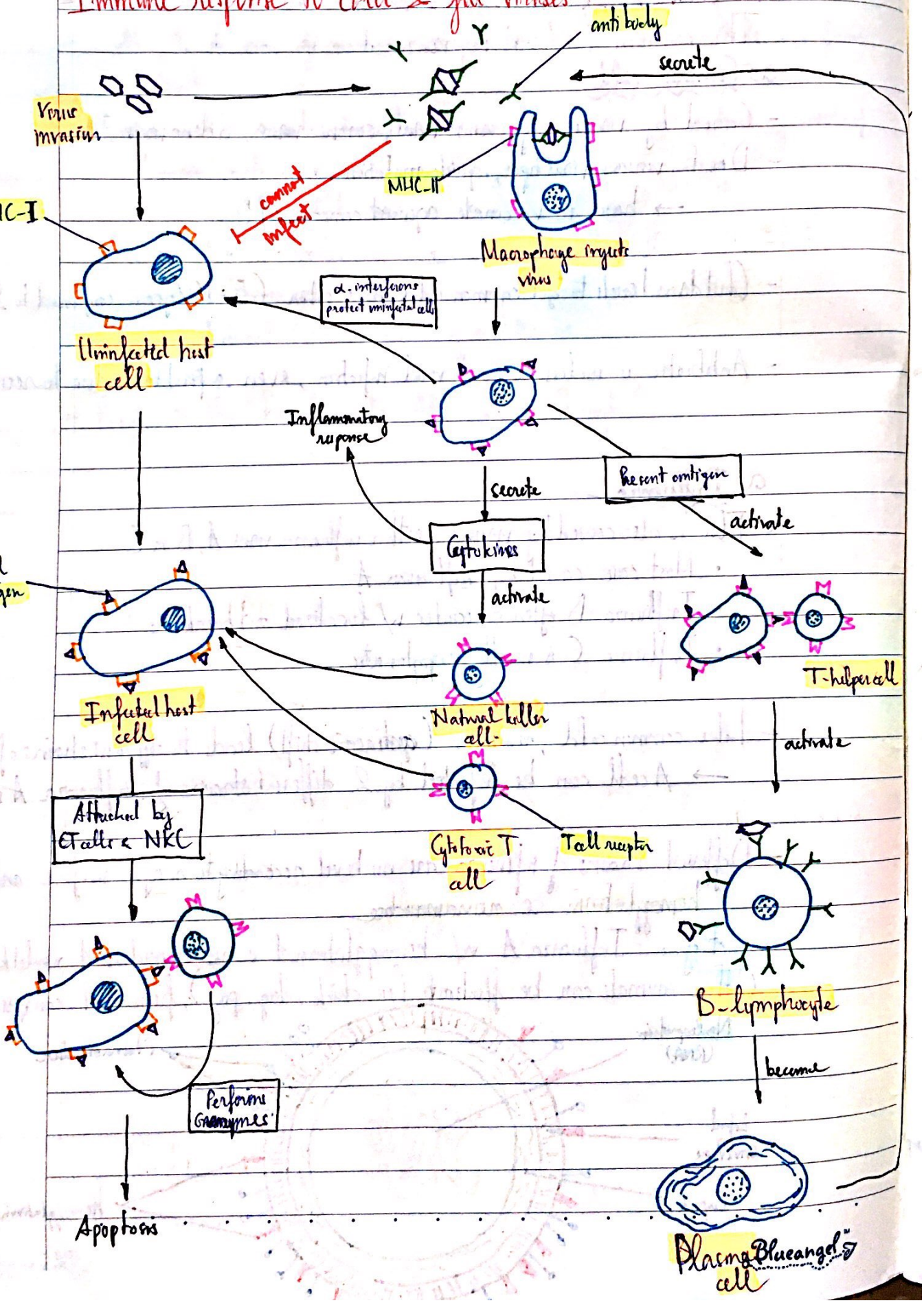
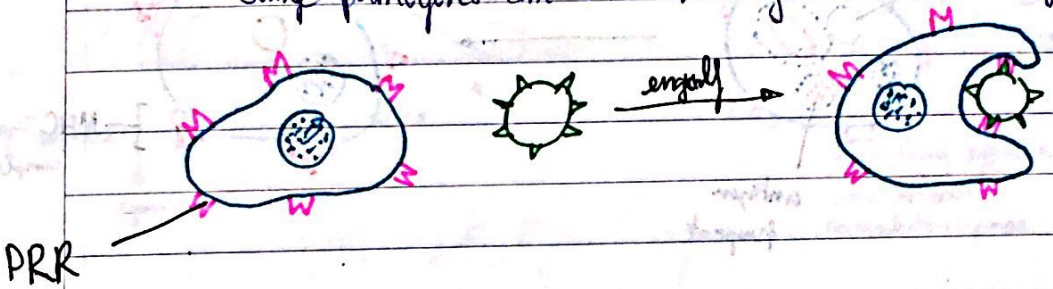
Immune response to cold & flu viruses



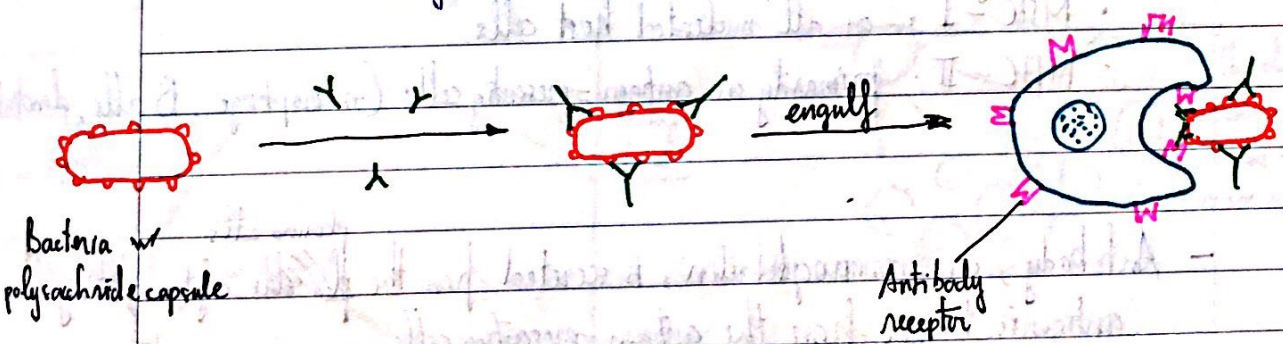
- On cells there are surface proteins (eg. MHC-I, MHC-II) which are able to attach to the viral antigens and present them onto the surface

- Plasma cells have extensive system of ER, which allows them to produce a specific protein call antibody (energy consuming)

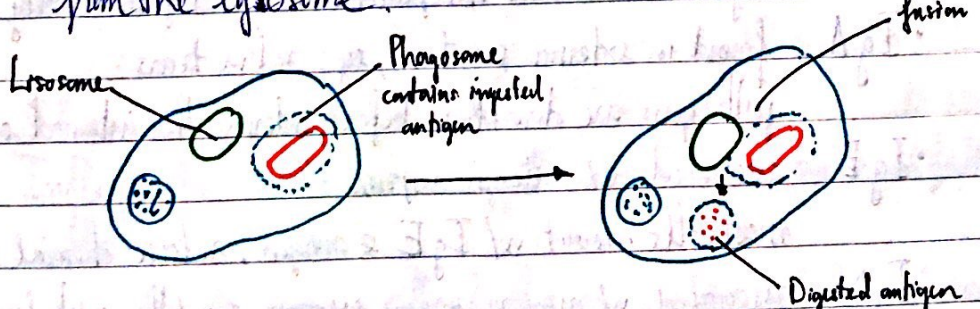
- Phagocytosis is a receptor-mediated process. There are pattern recognition receptors (PRRs) on the leukocyte, which can recognise the unique pathogen-associated molecular patterns (PAMPs)
  - Some pathogens can bind directly to the PRRs (eg. naked virion)



  - Others (eg. bacteria w/ capsules) must be coated w/ antibodies before ingestion



Once ingested, the antigen/pathogen is digested by enzymes & oxidants from the lysosome.



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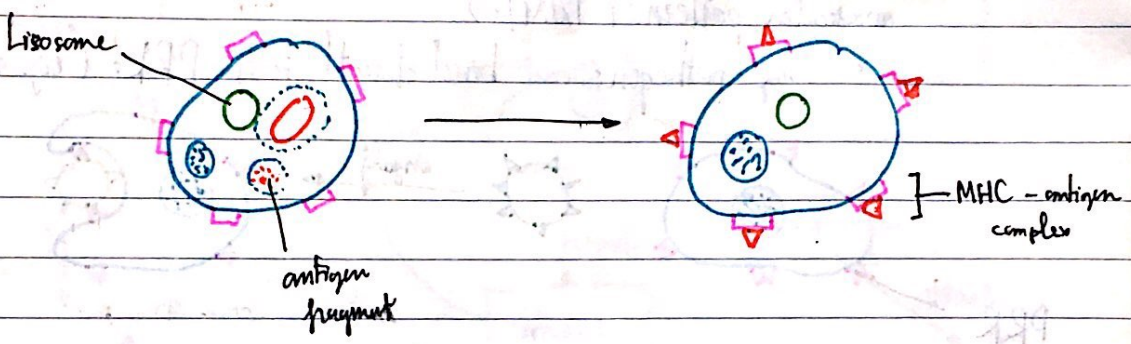
- Abt abant MHC ~~protein~~: the Major Histocompatibility Complexes are a family of membrane protein complexes encoded by a specific gene
These protein complexes were named since they play a role in rejecting transplants
Every nucleated cell contains MHC
MHC proteins combine w/ fragments of antigens that have been digested within the cell & the MHC-antigen complexes are inserted into the cell membrane by exocytosis. Free antigen cannot simply bind to MHC from the ECF on the cell surface



2 types of MHC molecules.
- MHC-I: on all nucleated host cells
- MHC-II: primarily on antigen-presenting cells (macrophage, B cells, dendriti

- Antibody, or immunoglobulin, is secreted from the plasma cells after getting a antigenic trigger from the antigen-presenting cells.
  - IgG: produced by secondary immune response, make up 75% of plasma Ig
    IgGs can also cross the placenta to give infant immunity
  - IgA: found in external secretion, eg. saliva, tears...
    pathogens are disabled before entering the internal environment
  - IgE: associated w/ allergic response
    mast cells interact w/ IgE & antigen, release chemical mediators
  - IgM: associated w/ primary immune response & w/ the antibodies that react to blo
  - IgD: appears on the surface of B cell, along w/ IgM, unclear functions

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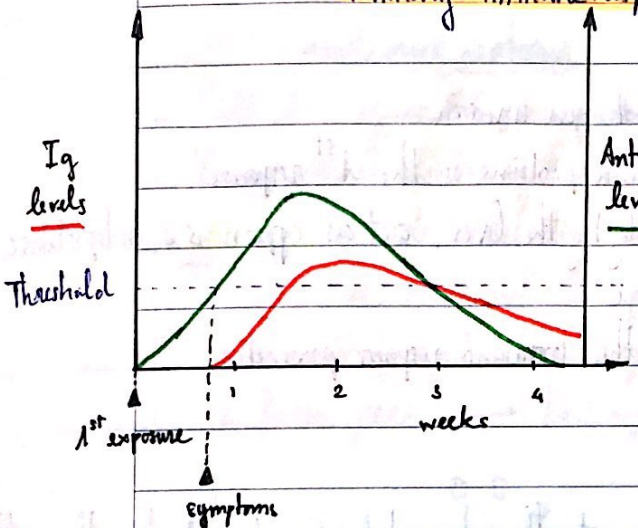
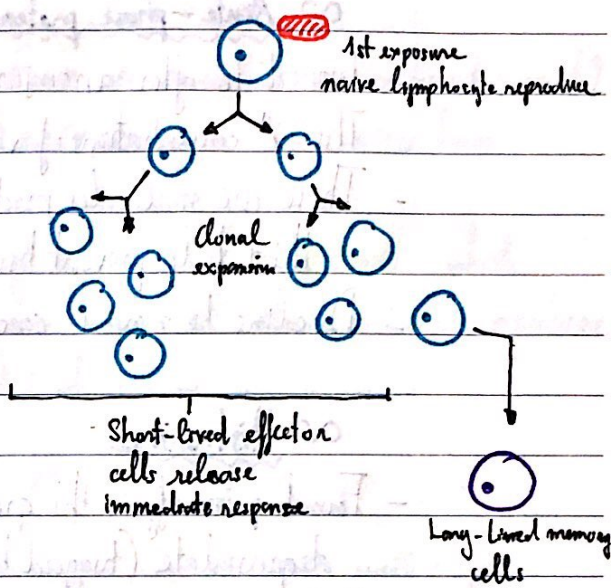
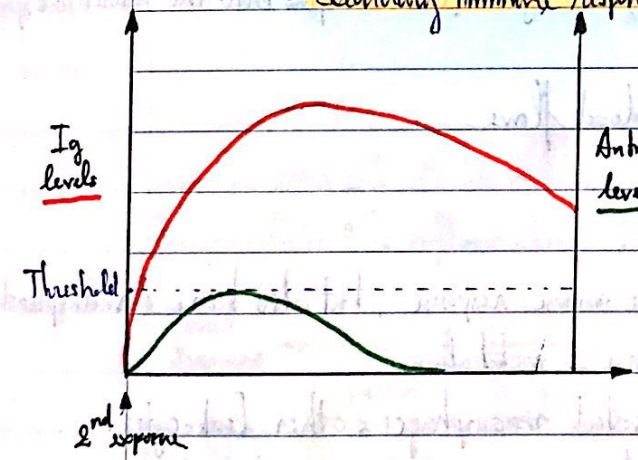
- After a B cell is activated by the antigen, it proliferates & differentiates into plasma cells, which in turn create more antibodies
After each successful repulsion, some memory cells remain behind, waiting for the next exposure to the same antigen.

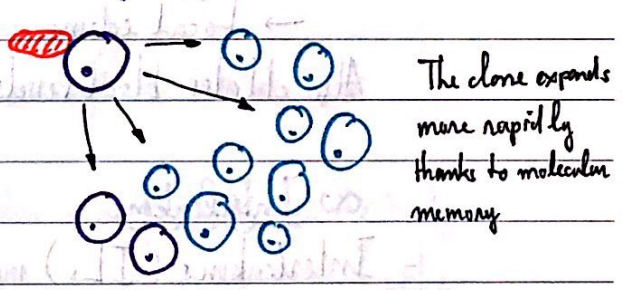
• Primary immune response: slow & low in magnitude





• Secondary immune response: rapid & larger





Cytokines create the Inflammatory response

- Inflammation is the hallmark of the innate immune system in fighting infection in damaged tissues:
  - Attracting immune cells to the site, along w/ chemical mediators
  - Producing a physical barrier to retard the spreading of infection
  - Promoting tissue repair when infection is under control

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- The inflammatory response is activated when the macrophages release cytokines, which:
  - Attract other immune cells, in turn release them am cytokines
  - ↑ Capillary permeability
  - Cause fever
- Some examples of chemical mediators:

~ Acute-phase proteins

- Immediate after an injury or a pathogen invasion
  The ↑ concentrations of various plasma proteins is the 1st response
- These are molecules produced mostly by the liver, act as opsonins & antiprotease that help prevent tissue damage
- Decline to normal conc. after the immune response proceeds

~ Histamine

- Found primarily in the granules of mast cells & basophils, is released when these cells degranulate (triggered by cytokines)
- Histamine opens pores in capillaries, allowing the plasma to flow into the interstitial space
  → Local edema
  Also dilates blood vessels to ↑ blood flow.

~ Interleukins

- Interleukins (ILs) mediate the immune response, but also have a widespread systemic effects on immune function & metabolism.
- IL-1 is secreted from the activated macrophages & other leukocytes:
  - Altering blood vessel endothelium → part of mucus formation
  - Stimulating production of acute-phase proteins by the liver
  - Inducing fever by acting on the hypothalamic thermostat
  - Stimulating cytokine & endocrine secretion

* Opsonin: protein that coats the pathogens so phagocyte can recognize & ingest

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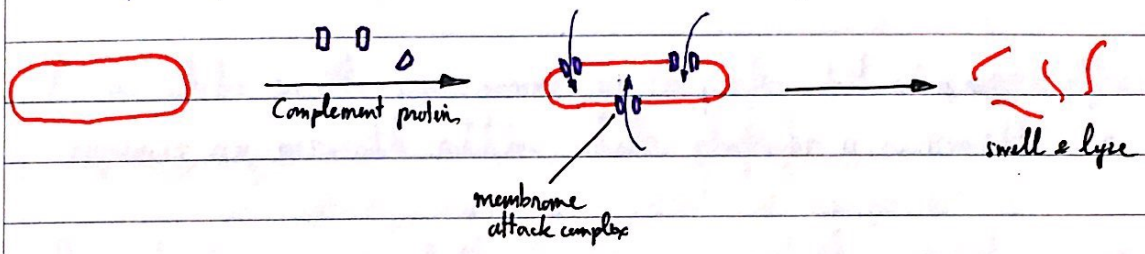
~ Bradykinin

- Kinins are a group of inactive plasma protein that involve in a cascade similar to the coagulation cascade, where the final product is bradykinin
- Bradykinin has the same function as histamine, but also stimulates pain receptors

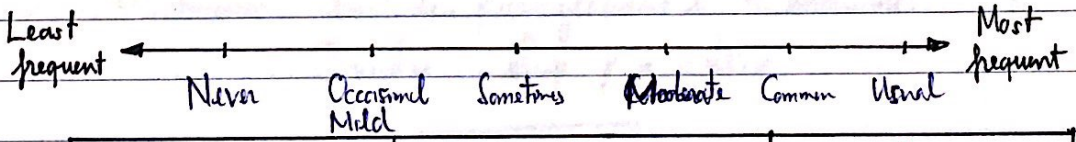
~ Complement proteins

- Collection of ≥ 25 plasma proteins & cell-membrane proteins (complement cascade)
  Various intermediates of the cascade act as opsonins, chemical attractants, mast cell degranulation factor
- The cascade ends w/ the formation of membrane attack complex, which is a group of lipid-soluble proteins that insert themselves into pathogen membrane & form pore → Pathogen (cell) swell & lyze



Symptoms of cold / flu

Immunological & inflammatory responses produce varying symptoms in the body:



Symptom	Cold	Flu
Headache	Occasional	Common
Stuffy nose	Common	Sometimes
Sneezing	Usual	Sometimes
Sore throat	Common	Sometimes
Cough / chest discomfort	Moderate	Common / severe
Fever	Mild	Usual, >38°C
Aches / Pain	Mild	Usual / severe
Fatigue	Sometimes	Usual (2 weeks)
Extreme exhaustion	Never	Usual

III) Treatments available for cold & flu

Analgesics / antipyretics

- Analgesic : ↓ pain associated w/ common cold (eg. ibuprofen)
  Antipyretics : ↓ fever (eg. paracetamol)

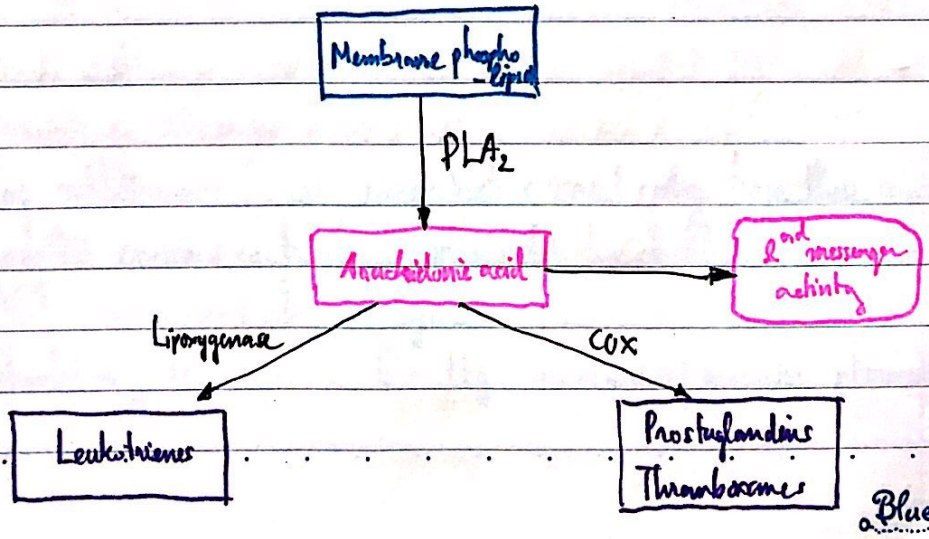
∞ Ibuprofen

- An NSAID that inhibits a class of COX enzymes
  The inhibition of COXs ↓ the production of PGE2 (pyrogenic)

- Numerous prostaglandins, eg PGE2 are pro-inflammatory
  → Ibuprofen also have anti-inflammatory effect
  → To relieve pain

- Aspirin works in the same manner as ibuprofen, but w/ a major difference:
  Aspirin is an irreversible inhibitor, while ibuprofen is a reversible one.

- Prostaglandins are one of the 2 major groups of the arachidonic acid-derived paracrines:
  - Leukotrienes : Secreted by certain types of WBC
    Play important role in inducing asthma
  - Prostanoids : Include prostaglandins & thromboxanes
    Involve in sleep, pain & fever



Paracetamol

- Unknown mechanism, some proposals:
  - Weak COX inhibitor, emphasized by the inability to have anti-inflammatory effects
  - Metabolite AM404 can ↓ pain & fever by affecting the thermoregulatory & nociceptor pathway
  - Metabolites NAPQI & pBQ, which activate a receptor involved in pain signalling called TRPA1, causing desensitization → ↓ pain

Side effects

- Paracetamol
  - Liver toxicity (overdose)

- Ibuprofen
  - GI effects
  - Headache
  - Dizziness
  - Salt & fluid retention
  - ↑ blood pressure

- Aspirin
  - Not recommended for <16yo (Reye's syndrome)

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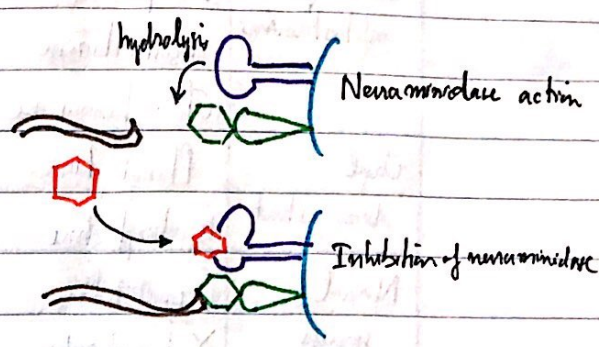
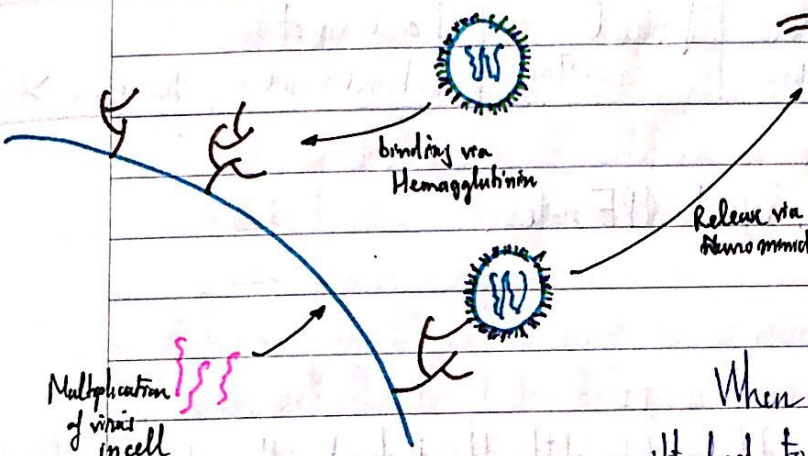
Antiviral medications for influenza

- Oseltamivir & Zanamivir are antiviral meds, working by inhibiting the enzyme neuraminidase on the virus surface

Neuraminidase promotes the release of the virus from infected cells to move within the RT





When a neuraminidase inhibitor is taken, the virus remain attached to the cell & more easily to be entrapped in respiratory secretion

- Oseltamivir is more advantageous since it can be formulated as oral capsule, whereas Zanamivir is available as powder for inhalation

- Both meds are taken twice/day for 5 days, best when taking this drug as soon as the flu symptoms appear

Antihistamines & Decongestants

- Sedating antihistamines, oral decongestants & nasal spray have these common features:
  - Limited evidence in treating common cold for children
  - Not recommended for <6yo
  - Should only be given to 6–11yo on advice of a doctor, pharmacist or nurse

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Drug class	Examples	Uses	Side effects
Sedating antihistamines	Diphenhydramine Brompheniramine Promethazine Chlorpheniramine	Dry respiratory secretion	Drowsiness, headache, blurred vision, xerostomia, dry mouth, urinary retention Paradoxical stimulation (rare) in children
Oral decongestants	Phenylephrine Pseudoephedrine	↓ nasal congestion	Restless, insomnia, headache, hypertension, palpitation
Nasal sprays	Oxymetazoline Xylometazoline	↓ nasal congestion	Local irritation Rebound nasal congestion if use >5 days

For dosing & counselling, refer to APF notes.

Cough expectorants & suppressants

- Cough can be caused by irritation of the throat due to inflammation, but often due to the mucus secreted from either throat/trachea or nose

- Treatment options
  - Expectorants: Facilitate the removal of secretion by ciliary transport & coughing
  - Antitussives: Depress cough reflex to reduce frequency & intensity of coughing
  - Mucolytics: ↓ mucus viscosity & facilitates expulsion of thick mucus secretion

Expectorants

- Steam inhalation: assist bringing up mucus from the chest. This might be due to ↓ edema & ~~the~~ viscosity of the mucus

- Guaifenesin: clears chest by loosening & ↓ viscosity of phlegm, ↑ vol of phlegm to make cough more productive

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- Ammonium chloride: may have an irritative action on the bronchial mucosa, thus ↑ mucosal fluid. Also might prevent pathogen adherence onto bronchial cells

- Bromhexine: may be called mucolytic, but little evidence. Also might help prevent pathogen adherence onto bronchial cells

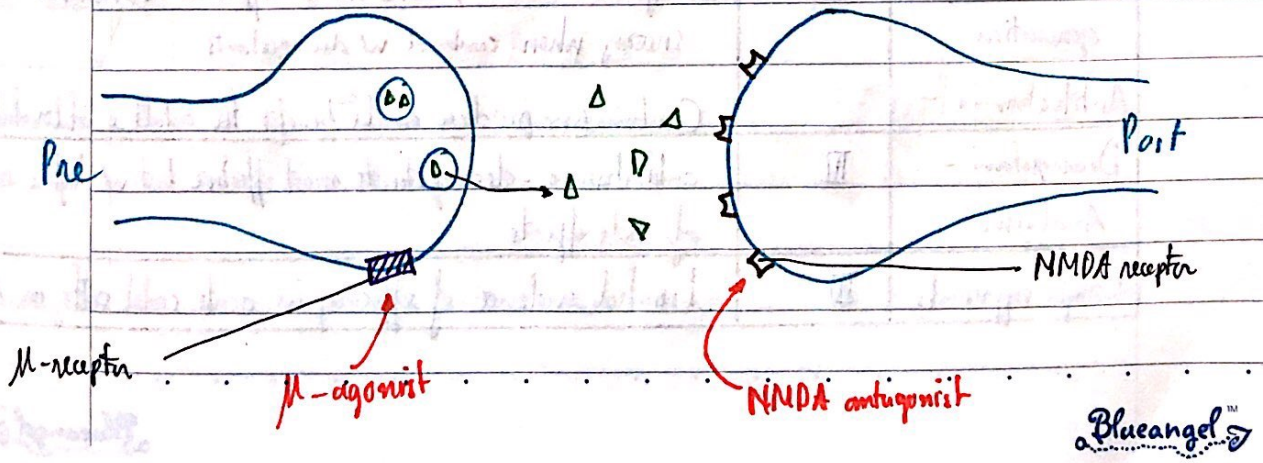
∾ Antitussives - μ-receptor agonists - NMDA antagonist

- Antitussive = reduce the need to cough:
  - Act centrally: in the cough center in the medulla
  - Act locally: in the throat to ↓ receptor sensitivity

- Antitussives should not be used for a chesty cough, as less mucus expulsion will actually lead to delay of recovery from an infection

- μ-receptor agonists suppress the cough reflex by ↓ the activity of the cough center, thus ↓ the releasing of glutamate
  Eg: codeine, dihydrocodeine, phelcodeine

- NMDA receptor antagonists displace the glutamate on the post synaptic NMDA receptors, which ↓ the cough reflex
  Eg: Dextromethorphan



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∞ Other remedies

- Ingredients commonly found in mixtures (honey, lemon) & lozenges (benzydamine, camphor, menthol) may have a local cough suppressant effect

Evidence of effectiveness

Category for reviewing evidence (National Health & Medical Research Council):

- I. Systematic review of all relevant randomized controlled trials
  → Highest level of evidence
- II. At least 1 properly designed controlled trials
- III. Well-designed pseudo-randomized comparative controlled trial
- IV. Case series

Meds	Evidence	Conclusion
Antibacterial Antibiotic	I	No more effective than placebo in adults & children
Ipratropium bromide	II	Modest efficacy for congestion & rhinorrhea in A&C
Nasal decongestants	II	Single oral dose modestly effective for short-term relief in adult
NSAIDs	II	Same efficacy in relieving discomfort but no clear evidence in easing respiratory symptoms in A&C
Antihistamines, 1st generation	III	Ineffective alone, have small effect on rhinorrhea & sneezing when combined w/ decongestants
Antihistamine-Decongestant-Analgesic	III	Combinations produce small benefit for adult & older children, antihistamine-decongestants most effective but w/ higher incidence of side effects
Cough suppressants	III	Limited evidence of efficacy in acute cold setting in A&C

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CAMs for cold & flu

CAM	Evidence	Conclusion
Echinacea Purpurea	I	Some evidence for early treatment efficacy in adults, but not in prophylaxis
Vitamin C	I	Failed to ↓ incidence of infection in A & C
Probiotics	I	May be more useful than placebo to prevent infection in <40yo
Zinc	I	↓ symptom severity & duration in healthy A & C when early in symptom onset
Garlic	II	May be more effective than placebo in adults
Heated, humidified air	II	Conflicting evidence in adults
Saline	II	Possibly beneficial for relieving symptoms of acute URTIs
Honey	III	No more effective than placebo on cough frequency, severity or sleep in early infection
Demulcent mucilages	IV	Little evidence to support efficacy of slippery elm or fenugreek

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IV) Sinusitis & rhinitis

Conditions leading to blocked nose

∞ Mucus in the nose

- Mucus production : lubrication & engulfing foreign bodies
  The nasal mucosa is highly vascularized, & these capillaries can be inflammed by chemical mediators eg. interleukins

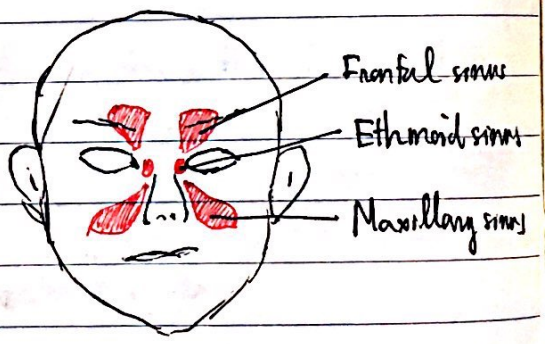
- When blood vessels in the nasal cavity became inflammed, they became more permeable → fluid mix w/ mucus leading to nasal congestion or a "post-nasal drip" (mucus runs back to the lungs)

- Tears from the eye drain into the nasolacrimal duct to the nasopharyngeal region
  → Also contribute to rhinorrhea & post-nasal drip

- These blood vessel in the nose are richly innervated w/ sympathetic fibers, containg α_1 & α_2 receptors which constrict the blood vessels
  → Decongestants are α_1 & α_2 agonist

∞ Sinusitis

- Sinusitis = inflammation of the sinuses, caused by mold, bacteria or fungi, or
- by allergic reactions



Often people get sinusitis of a bacterial nature following to (or secondary to) an acute URTI such as common cold, In this case, often caused by bacteria such as streptococcus

- Acute sinusitis lasts < 3 weeks, whereas chronic sinusitis lasts longer than this

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- Symptoms could be malaise, fever/chills & yellow/green purulent nasal discharge
Unlike common cold, ppl w/ acute sinusitis don't tend to have a great deal of nasal discharge, but obstruction in the sinus can cause sinus pain & headache

- Chronic sinusitis may be caused by structural abnormalities of the nose, eg broken nose, or growth of nasal polyps
Alternatively, it may be infective, caused by a bacterial or fungal infection

~ Rhinitis

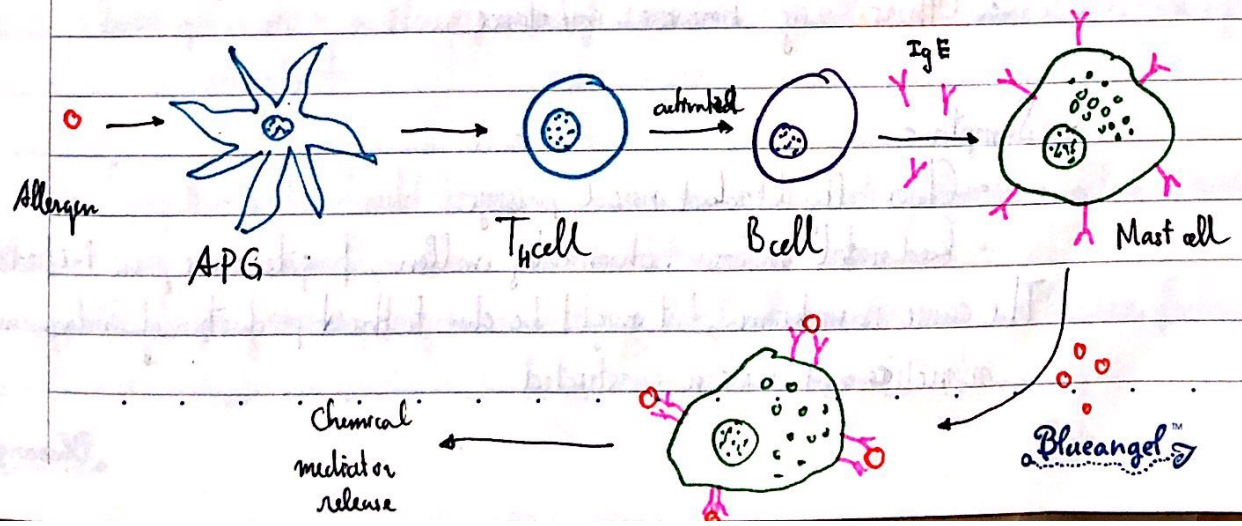
- Rhinitis = inflammation of the nasal mucosa
Can be annoy, decrease quality of life especially when associated w/ nasal polyps

- 2 types: allergic & non-allergic

~ Allergic - rhinitis

- Also called hay fever & can be: {seasonal / perennial

- Symptoms:
  - Sneezing
  - Nasal symptoms; eg: itchy, discharge, congestion, impaired smell
  - Ocular symtomes; eg: itchy, watery, conjunctival symptoms
  - Additional: headache, irritability, ↓ appetite, insomnia, coughing, wheezing



- These IgE mediated responses are not restricted to allergic rhinitis
There are actually some ppl are genetically more hypersensitive to allergens than others
This is called "atopy": a genetically determined state of hypersensitivity to environmental allergens

Types of allergic reactions / hypersensitivity
- Type 1: associated w/ the IgE antibody e.g group of diseases, eg asthma, hayfever,..
- Type 2: the antibody produced by the immune response bind to antigens on the patient's own cell surface (could be intrinsic or extrinsic) eg blood type
- Type 3: occurs when there is accumulation of antigen-antibody complexes that are not adequately cleared by innate immune cells → inflammatory response
- Type 4: delayed type as the reaction may takes days to develop. It is not antibody-mediated, but rather a cell-mediated response
- Type 5: a distinction from type 2, the antibodies may bind to a cell's surface receptors, thus impair cell signalling

Non-allergic rhinitis

6 types of non-allergic rhinitis:
- Vasomotor (irritant) rhinitis: from smoke, perfume, dropped t°, alcohol, spice..
- Infectious rhinitis: often viral, sometimes bacterial
- Drug induced: rebound congestion, drug side effects
- Structural rhinitis: broken nose, nasal birth defects
- Nasal polyps: growth on mucus membranes of nose
- Others: eg. hormone imbalance

- Symptoms:
- Chronically blocked nasal passage
- Red nasal mucosa, chronically swollen, fragile areas prone to bleeding

The cause is unknown, but might be due to the ↓ production of endogenous , thus, cannot remain constricted.

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∾ Rhinitis caused by decongestant overuse

- Limitation about nasal sprays is that they should only be used for short-term (i.e. 3-5 days in a row). Overuse of such medications can cause rebound congestion when stopping the treatment (rhinitis medicamentosa)

If a person wants to get rid of the rebound congestion, there is no other ways than quitting and stop using the nasal spray, along w/ some other therapies to relieve the symptom

Treatments available for each conditions

∾ Mucus in the nose

- The leaky capillaries in the nose due to dilation make the nose full of fluid
  → α agonists causing vasoconstriction are an appropriate treatment

- α agonists are used extensively as nasal decongestants in patient w/ allergic or vasomotor rhinitis & in acute rhinitis in URTIs
  These drugs ↓ the airflow resistant by acting (constricting) the blood vessels that have erectile function.
  The receptors that mediate this effect appear to be α_1 receptors
  α_2 receptors mediate the contraction of the arterioles that supply nutrition to the nasal mucosa, where extensive constriction of these vessels may lead to structural damage

- Phenylephrine is a α_1-agonist, which can be administered topically & orally
  Pseudoephedrine is a stereoisomer of ephedrine but with less cardiac & CNS side effect & less potent

- Sympathomimetic should be used w/ caution in patients w/ hypertension & enlarged prostate, and is contraindicated w/ MAO inhibitor takers.
- Nasal sprays containing oxymetazoline & xylometazoline also work in the same fashion

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∞ Sinusitis

- Paracetamol & ibuprofen for pain & fever relief
- Saline nasal spray/drop. Salt water irrigation can be used for clearing excess mucus from nose & sinus areas to assist nasal drainage
  - Mild to moderate: nasal spray +/- eucalyptus oil/tea tree oil/xylitol
  - Moderate to severe: cleansers / saline flush thru the sinuses
- If it is a bacterial sinusitis, antibiotics (eg. amoxicillin, ampicillin) can be use w/ advice of a doctor. Do not use antibiotics for a viral infection
- Surgery would be considered in patients w/ persistent condition, to structurally remove the damage tissue / polyps, where appropriate treatments shown no benefit

- Antihistamines, topical & systemic steroids shown no benefits;
No data to support the efficacy of topical & systemic decongestants to treat sinusitis.

- Non-pharmacological methods:
  - Rest, drink water & non-alcoholic fluids
  - Avoid exposure to cigarette smoke
  - Steam inhalation

∞ Allergic-rhinitis

Any treatment for hay fever tends to work more effectively if given before exposure to allergens & the release of pro-inflammatory chemical mediators
→ Advise people to monitor weather forecasts & if the pollen count is to be high, antihistamine should be taken

For some people, taking medication daily before & during spring may be required

Antihistamines

- These meds work by binding to histamine H_1 receptors → prevent histamine from binding to H_1 receptors & producing effect eg. vasodilation & inflammation

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- Antihistamines were thought to be H_1 antagonists, but it is most likely act as inverse agonists

- H_1 receptors appear around the body, particularly on immune cells & on cells in mucus membranes in the RT & eyes. Also in the brain, where they play an important role in wakefulness → Older generation of antihistamines can cause sedation. Newer antihistamines (eg. cetirizine, fexofenadine, loratadine) have less CNS effect.
These antihistamines also have significant anticholinergic effects, which may cause drying up nasal secretions.
The antihistamines in the later generation are similar in effectiveness, if a person doesn't get from one, then may from another

- Antihistamines are available in different formulations:
  - Tablets
  - Nasal sprays
  - Eye drops

- Types of antihistamine (sedating)

Subclass	Drug	Adverse effects	Pregnancy	Children
Alkylamines	Brompheniramine	Sedation, anticholinergic, low incidence of GI effects, CNS stimulation	Not available as a single ingredients	
	Chlorpheniramine			
	Dexchlorpheniramine		Safe	>2yo
	Pheniramine			>5yo
Ethanolamines	Diphenhydramine	Significant sedative, anticholinergic, GI incidence	Safe	>6yo
	Doxylamine			>12yo
Phenothiazines	Alimemazine	Significant sedative, anticholine	Safe but avoid close to delivery	>2yo
	Promethazine – HCl / theoclate	resp. depression, lowered seizure threshold.		>2yo
				>5yo
Piperazines	Cyclizine	Slight sedative	Safe	>6yo
Piperidines	Cyproheptadine	Sedative	Safe a Bluear	>2yo

- Not all sedating antihistamines are used to treat hay fever as the hay fever symptom relieving characteristic may not be as strong as the side effects
  Eg. Dimenhydrinate for antiemetic
  Doxylamine for insomnia

- Less sedating antihistamines are:
  - Cetirizine
  - Fexofenadine (metabolite of Terfenadine)
  - Loratidine
  - Desloratidine (metabolite of Loratidine)
  - Certrizine
  - Levocetrizine (isomer of Cetrizine)

- Some other medicines that have antihistamine activity (not actual H_1 antagonists except ketotifen are Azelastine Levocabastine & Sodium cromoglycate
  - Azelastine: Stabilizing mast cells
  - Levocabastine: H_1 antagonist
  - Sodium cromoglycate: Stabilizing mast cells

Corticosteroids

- These medicines are often given intranasally, acting at glucocorticoid receptors agonist
  Nuclear activation leads to dimerization of the agonist/receptor complex to function as a transcription factor
  We are aiming for the reduction of pro-inflammatory proteins (eg COX) and the increase of anti-inflammatory proteins (eg annexin 1)
  The process of altering protein synthesis takes time
  → Not immediate relief like nasal decongestant, but may takes a few days to achieve max effect.

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- Most common effect of steroid treatment is epistaxis (nose bleed), when higher doses of intranasal steroid are used.

- Corticosteroid drugs:
  - Fluticasone
  - Triemcinolone
  - Ciclesonide
  - Beclometasone
  - Budesonide
  - Mometasone

- Intranasal corticosteroid is substantially proven to provide significantly greater relief of nasal congestion than oral antihistamines
  Intranasal corticosteroid is also known to reduce ocular symptoms of allergic rhinitis, most likely by ↓ inflammation in the nose, this normalizes an excess in stimulation of a reflex that occurs w/ allergic rhinitis whereby inflammation in the nose produces ocular symptoms

- Allergic rhinitis may not usually be required to be reffered to a doctor, unless the patient cannot take the medicines or there is no relief from appropriate treatment
  A doctor may prescribe montelukast (for asthma) for relief of nasal congestion.

∾ Non-allergic rhinitis

- Refer to nasal sprays of α agonist discussed in the "Menu in the nose"

∾ Rhinitis caused by decongestant overuse

- Nasal decongestant can be avoided and replaced w/ oral decongestant
  Eg: Pseudoephedrine can be taken up into the nerve terminals in exchange for NA.

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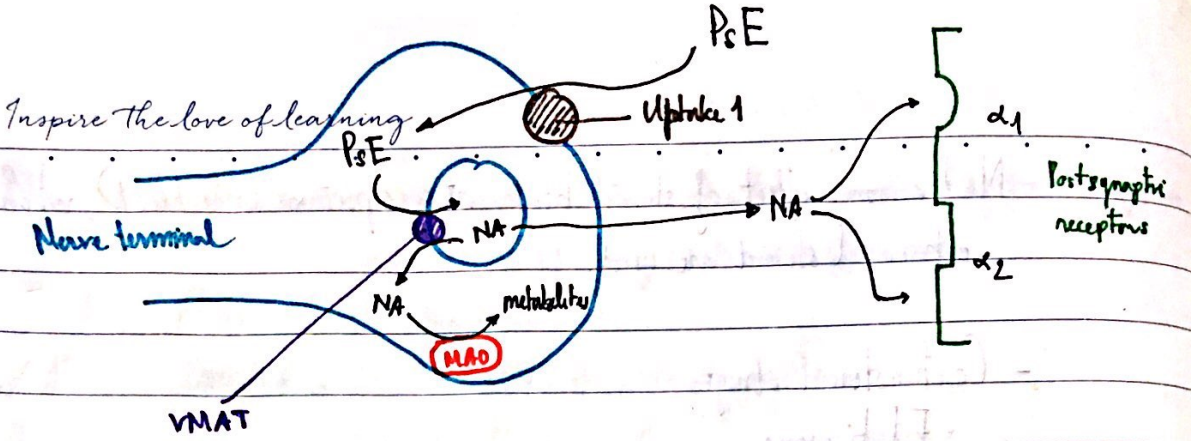
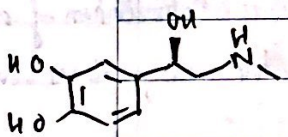


- Most important function of Pseudoephedrine is the resistance to MAO breakdown, and it is excreted 96% in the urine (unchanged)

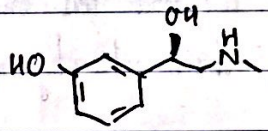
Pseudoephedrine resembles amphetamine & methamphetamine, which cause CNS stimulation & insomnia

→ Abuse potential & side effects of pseudoephedrine, Phenylephrine can be used

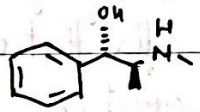
However, no supporting document for efficacy of Phenylephrine as a nasal decongestant when administered orally. Most likely reason is that, Phenylephrine is an MAO substrate & only 3% is excreted unchanged in the urine



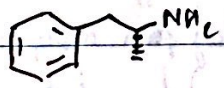
Adrenaline



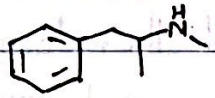
Phenylephrine



Pseudoephedrine



Amphetamine



Methamphetamine

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Week 2 5/3/2018

I) Pathophysiology, Diagnosis & Assessment of Asthma

Introduction

- Asthma is one of the most common chronic diseases worldwide
Prevalence in many countries, especially in children, due to environmental & lifestyle change

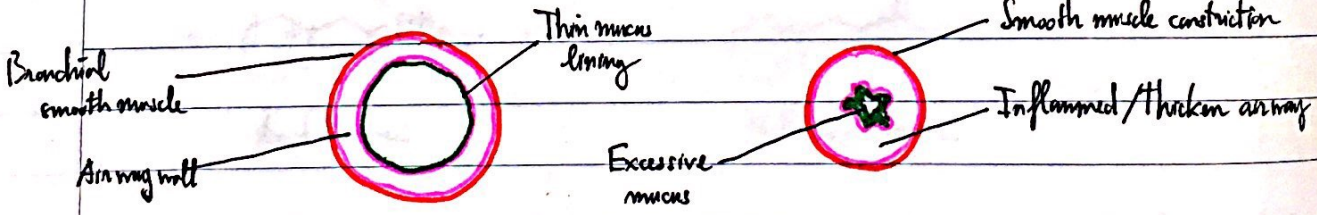
Patients w/ asthma are generally managed in the primary care or outpatient setting
Poor controlled asthma may result in hospitalization or admission to the emergency department
In the event of respiratory failure, patient may require intubation or mechanical ventilation

Pathophysiology : Overview

What happens in asthma

- Asthma is an obstructive respiratory disorder w/ genetic & environmental origins, characterized by the increased sensitivity to variety of stimuli, airflow obstruction which the bronchioles nearest to the trachea is most affected.

In an individual w/ asthma, the respiratory system is hyper-responsive. To specific triggers, inflammation, enhanced mucus secretion & smooth muscle constriction are observed in the bronchioles



Symptoms

- Dyspnea
- Wheezing (confirm w/ stethoscope)
- Difficulty expiration
- Chronic cough (often at night or early morning)
- Chest tightness & shortness of breath

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- Not all symptoms appear at the same time, and some symptoms may not be indicative
  Eg: Cough may be the only symptom,
  Wheezing can be caused by turbulent air flow due to narrowed airway
In young children, the symptom may be different: breathe by stomach, have a sore tummy or chest.

- Asthma can come gradually or suddenly and at any stage of life.
  - Had asthma in the past, it can return any time
  - A child w/ asthma symptoms may not have any asthma later

∞ Triggers

- Asthma is recurrent & reversible to a degree, as the triggers consistently exist and there are treatment to control asthma (although not a cure)
Triggers are generally non-noxious stimuli that don't affect non-asthmatic:
  - Allergen, eg. pollen, dust
  - Drug triggers, eg β blocker, aspirin
  - Exercise, cold air
  - Irritants, chemicals, eg sulphites, ammonia
  - Pollutants
  - Stress & emotional distress - however, not the emotion itself, but the response to that emotion, eg laughing, crying

∞ Atopic & Non-atopic asthma

- Atopic asthma, or genetically originated asthma, is associated w/ the development of the IgE antibodies in response to allergens
IgE is predisposed after the 1st contact w/ the allergen
  → Immune response on later exposure to the same allergen
- This type of asthma is associated w/ a positive skin response to allergen, often seen w/ other atopic skin condition (eg. eczema, allergic rhinitis)

- Non-atopic asthma, or non-allergic, is seen w/ a negative family history of asthma & skin test to allergens
Exposure to workplace & environmental factors is thought to cause pathological changes, resulting in restricted airways
There is often IgE-independent effects, eg. bronchial hyperactivity due to a dominant parasympathetic action
Localised IgE production & ↑expression of activated immune cells in the airways

Acute asthma : early & late phases

∞ Pathogenesis

- Players in the game :
  - Mast cell : release chemical mediators (eg histamine, PGD, ..)
  - IgE : can form complex w/ mast cells
  - Eosinophil : acytotoxic & phagocyte & granulocyte
  - Dendritic cells : antigen presenting cells
  - T helper cells : T_h-1 – cell-mediated inflammation
    T_h-2 – antibody-mediated inflammation

- In normal physiology, in the lung, T_h-1 is predominant. However in atopic asthma, T_h-2 cells are upregulated, thus lead to an imbalance between cell- & antibody-mediated event.

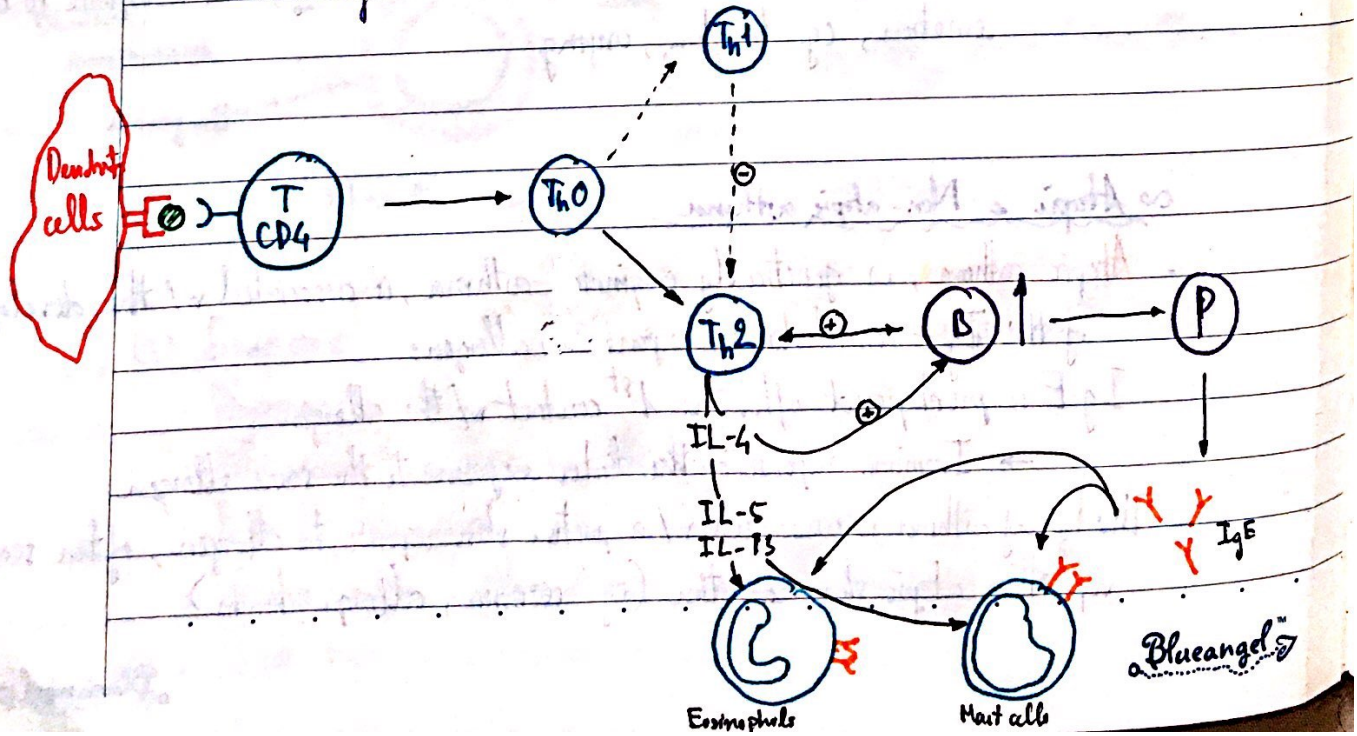

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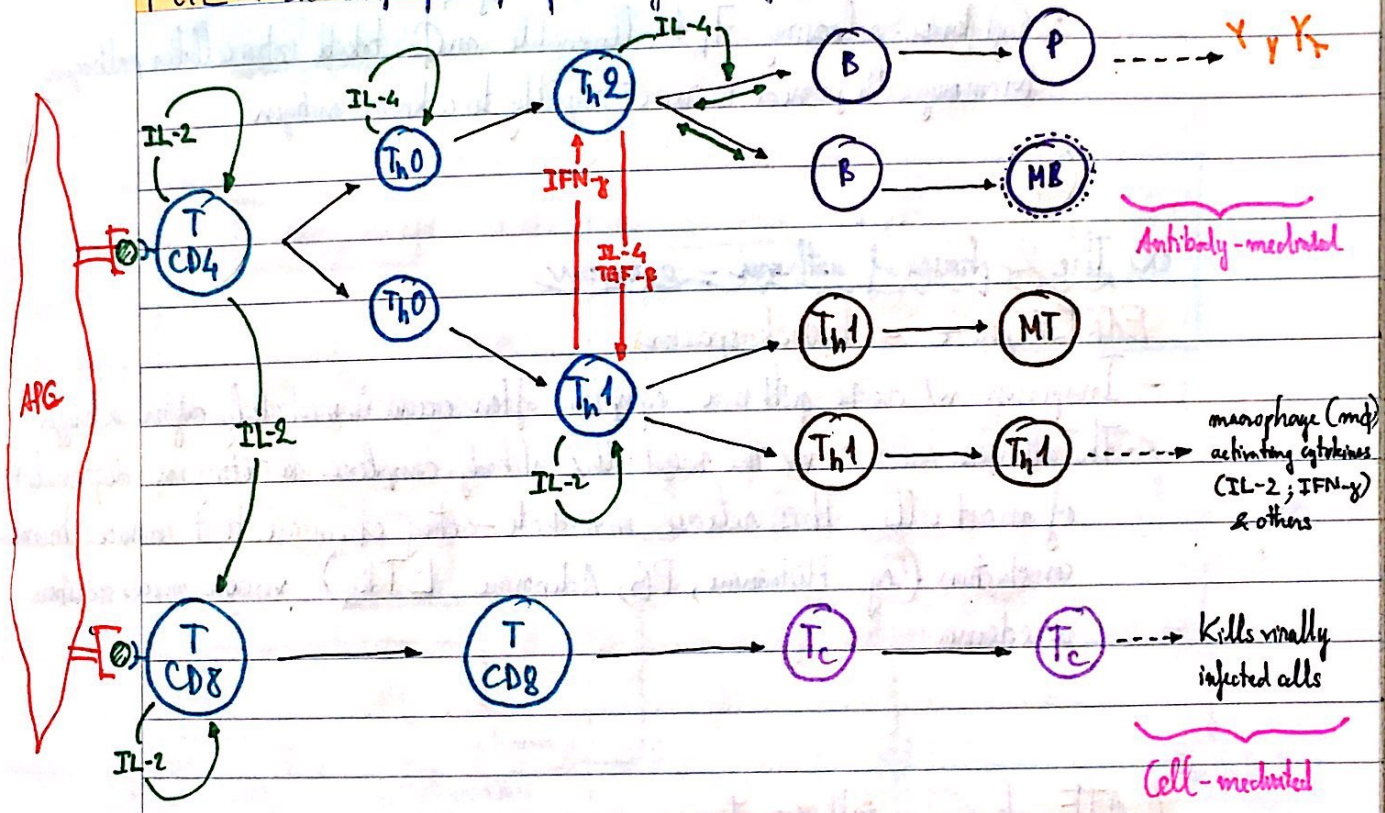
Diagram: $CD4^+$ T cell interact w/ the antigen/allergen from the APC, differentiate into the development of ThO cells, which gives rise to the Th2 cells

Th2 cells release chemmediators, generating a cytokine environment which switches B cells into plasma cells and produce IgE.

These antibodies binds to granulocyte, eg mast cells & eosinophils to form complex.

Th2 cytokines also attract eosinophils to the mucosal surface and induce IgE receptor expression on mast cells & eosinophils (eg. IL-4, IL-13) or promote differentiation & activation of the eosinophils at bone marrow (eg IL-5)

FULL but simplified for phases of leukocyte activation:



→ inhibition

→ stimulation

→ pathway

Antigen presentation

Clonal expansion & maturation

Induction phase

Effector phase

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The different functions of cell- & antibody-mediated reactions:

- Antibody provides:
  - More selective complement activation
  - More effective pathogen phagocytosis
  - More effective attachment to multicellular parasites, ↑ their destruction
  - Direct neutralization of some viruses & bacterial toxins

- Cell provides
  - $CD8^+$ T cells (Cytotoxic T_c) kills virally infected cells
  - Cytokines - releasing T_h1 cells enable mΦ to kill intracellular pathogen
  - Memory cells primed to react rapidly to a known antigen

The 2 phases of asthma - overview

EARLY phase - bronchospasm

- In person w/ acute asthma, symptoms often occur immediately after a trigger. The allergens interact w/ the mast cell/antibody complexes resulting in degranulation of mast cells. This release immediate-acting chemicals that induce bronchoconstriction (eg. Histamine, PG_2, Adenosine, LTB_4), viscous mucus secretion, & edema

LATE phase - inflammation

- The symptoms can be experienced much later than in early phase.
  Both the early and the late phases are triggered by the same allergen, at the same time, but due to the need for other mediators to be synthesized, the effect is delayed for several hours
  Furthermore, a large proportion is due to the involvement of other immune cells (eg. eosinophils) which need to be synthesized, activated & recruited to the airway.

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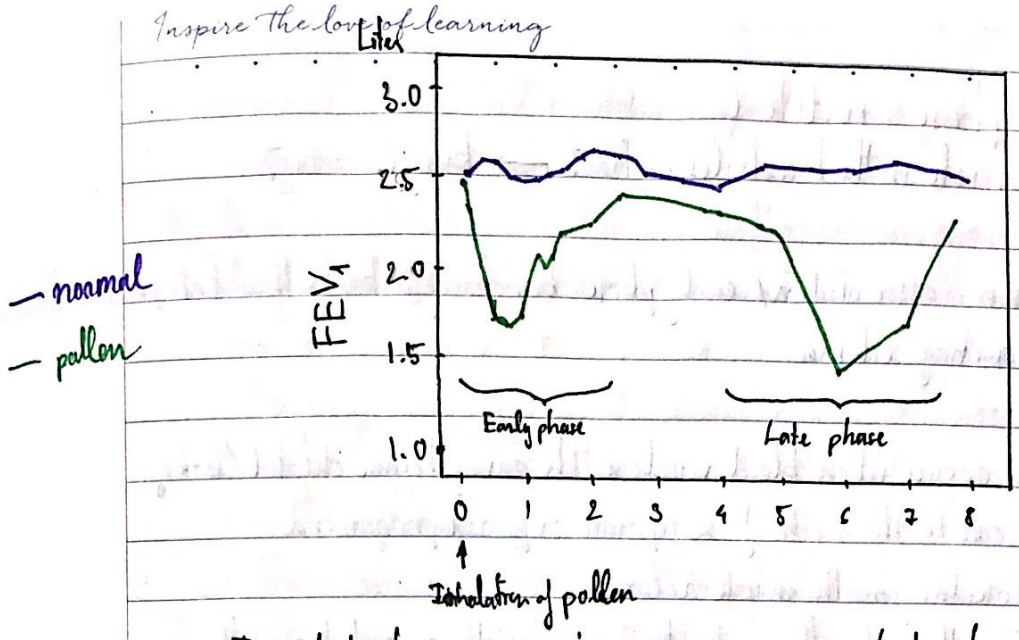

Immediate phase | Late phase

Triggers

Mast cells, monomuclear cells

Spasmogens cysLT?, Histamine, PGD_2

Chemotaxins Chemokines

Delay

- Infiltration of cytokine-releasing T_H2 cells & monocytes
- Activation of inflammatory cells, particularly eosinophils

Mediators cysLT, neuropeptide?, NO? adenosine?

EMBP, ECP*

Epithelial damage

Airway inflammation

Airway hyper-reactivity

bronchospasm

Bronchospasm, wheezing, coughing

* EMBC : Eosinophil major basic protein
ECP : Eosinophil cationic protein

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Early phase in detail

- Smooth muscle in the bronchioles contract → bronchoconstriction

- Histamine is associated w/ early phase bronchoconstriction & then late phase inflamm & airway edema

Edema occurs when blood vessels in the airway become dilated/leaky
Edema can be the result of 2 separate or paired phenomena
- Vascular smooth muscle relaxation
- Endothelial cell contraction → provide gaps between cells
  ⇒ Swelling

- Airway PG (eg PGD_2) cause bronchoconstriction, edema, ↑mucus secretion
Goblet cells are specialized to produce mucus
Submucosal glands also produce mucus, & this luminal layer of mucus provide an important homeostasis/housekeeping role in cleaning & filtering the air.
Ciliated cells rhythmically push the mucus upward to be expectorated or swallow

- Leukotrienes, are like PG in away that they are also phospholipid-derived inflamm mediators, released by leukocytes
Cysteinyl LTs (eg: LTC_4, LTD_4, LTE_4) are generated in mast cells, basophils mΦ & eosinophil & act at CysLT1 & CysLT2 receptors to stimulate bronchoconstriction, ↑mucus secretion, ↑vascular wall permeability, edema & inflammation
LTB_4 are powerful attractant to neutrophils & mΦ

- Platelet activating factor (PAF) is released following interaction between the IgE expressed on mast cells & the allergen
Apart from being a chemoattractant, PAF can cause bronchoconstriction, ↑mucus

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edema, promote inflammation & hyper-responsiveness

- An allergen interaction w/ IgE-bound high affinity receptor on mast cells → synthesis & release of longer-acting mediators:
  - LTB_4
  - PAF
  - IL (eg. IL-13, IL-4)
  - mΦ inflammatory protein 1a
  - Tumor necrosis factor a (TNF-a)

These chemotaxins & chemokines attract leukocytes to the airway

Mediator	Bronchoconstriction	Mucus secretion	Edema
Histamine	✓	✗	✓
PG	✓	✓	✓
Cys LT	✓	✓	✓
PAF	✓	✓	✓

Late phase in detail

- Recruitment of other immune cells to the airway & the release of chemical mediators from these cells results in the manifestation of a second set of symptoms

Apart from these chemical mediators in the early phase, there are additional longer-acting toxic mediator, eg:

- Neuropeptides (eg substance P & neurokinin A), released from sensory neurons to contribute to inflammation
- Tissue remodelling mediators (eg ECP, EMBP, eosinophil-derived neurotoxin, & eosinophil peroxidase) which cause epithelial damage
- Fibrogenic & growth factors (↗ hyperplasia (mucus cells) & hypertrophy) of fibroblasts, smooth muscles...

- The release of these so-called "cotoxins" promotes proliferation of fibroblast & fibro
  increased collagen disposition, hyperplasia & hypertrophy of smooth muscle &
  necrosis of epithelial cells
  → Pathological airway remodelling and could be permanent

Well-controlled asthma usually doesn't have eosinophilia → no remodelling
→ Corticosteroid treatment for life long asthma

Chronic asthma

- Chronic asthma refers to the repeated episodes of the early & late phase reaction w/ can lead to remodelling of the airway & worsening of the symptoms, such that response in the acute episode is exacerbated.

Monitoring symptoms is key to understanding whether a patient can develope chronic asthma.

- Reasons for the development include:
  - lack of diagnosis / treatment
  - insufficient patient regconition
  - inappropriate medication

Treatments for asthma will be discussed later in this week

Medication - induced asthma

2 types: predictable & unpredictable

- Predictable: known pharmacological properties of the medication (dose dep)
  - β-blocker (including eyedrop)
  - Cholinergic agent
  - Cholinesterase inhibitor

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- Unpredictable : reaction is not related to the dose of the medication
  - Carbamazepine (epilepsy)
  - Parenteral drugs (penicillin, hydrocortisone, aminophilline, N-acetyl cysteine)
  - Preservative (bisulphite, metabisulphite, benzalkonium chloride)

- About 3-11% of adult w/ asthma is triggered by NSAIDs. Impaired PGE_2 synthesis & excessive LT may contribute. No convincing evidence support the relationship between aspirin-induced asthma & IgE mediated mechanism.
Aspirin intolerance along w/ asthma & nasal polyps, flushing & rhinorrhea can occur within a few minutes from hour of administration of aspirin. These ppl should use paracetamol instead.
Some ppl w/ AIA may also have mild reaction to higher dose of paracetamol (1-1.5g).

LT receptor antagonists are used for long-term control of AIA, but should be avoided w/ aspirin & NSAIDs.

Diagnosis

How

- Go for a GP & have a check on family history of atopy, recent viral or trigger exposure
- Provisional diagnosis of asthma if all the symptoms are present:
  - Wheezing + Coughing
  - Breathing difficulty
  - No sign to suggest alternative diagnosis
  - Response to bronchodilator demonstrated on a spirometer before & after taking β_2 agonist

- There is no single reliable test nor any standardized asthma diagnosis & can be very hard to diagnose a 0-5 yo:
  - Wheezing & coughing are common in children

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- Spirometer is inapplicable
- High proportion of children respond to bronchodilator don't have asthma later in life

A diagnosis should only be made when there are substantial signs of airflow limitation & cough is not the only predominant symptoms

Using a spirometer

- Spirometry measures:
  - FEV_1
  - FVC
  - How quickly the air was expelled from the lungs

- Spirometer technique is crucial for most reliable readings
  Measurement both before & after administration of a short acting β_2 agonist will:
  - Determine airflow limitation & its degree
  - Monitor effectiveness of treatment
  - Demonstrate the presence & reversibility of airflow limitation
  - Provide feed back

- Diagnosis of asthma can be made if ALL of the following apply
  - Person has variable symptoms
  - Expiratory airflow limitation has been demonstrated
  - " shown to be variable
  - No suggestive alternative diagnosis

- On the spirometry diagram, there are usually 2 curves:
  - Flow / volume curve (spiral)
  - Volume / time curve

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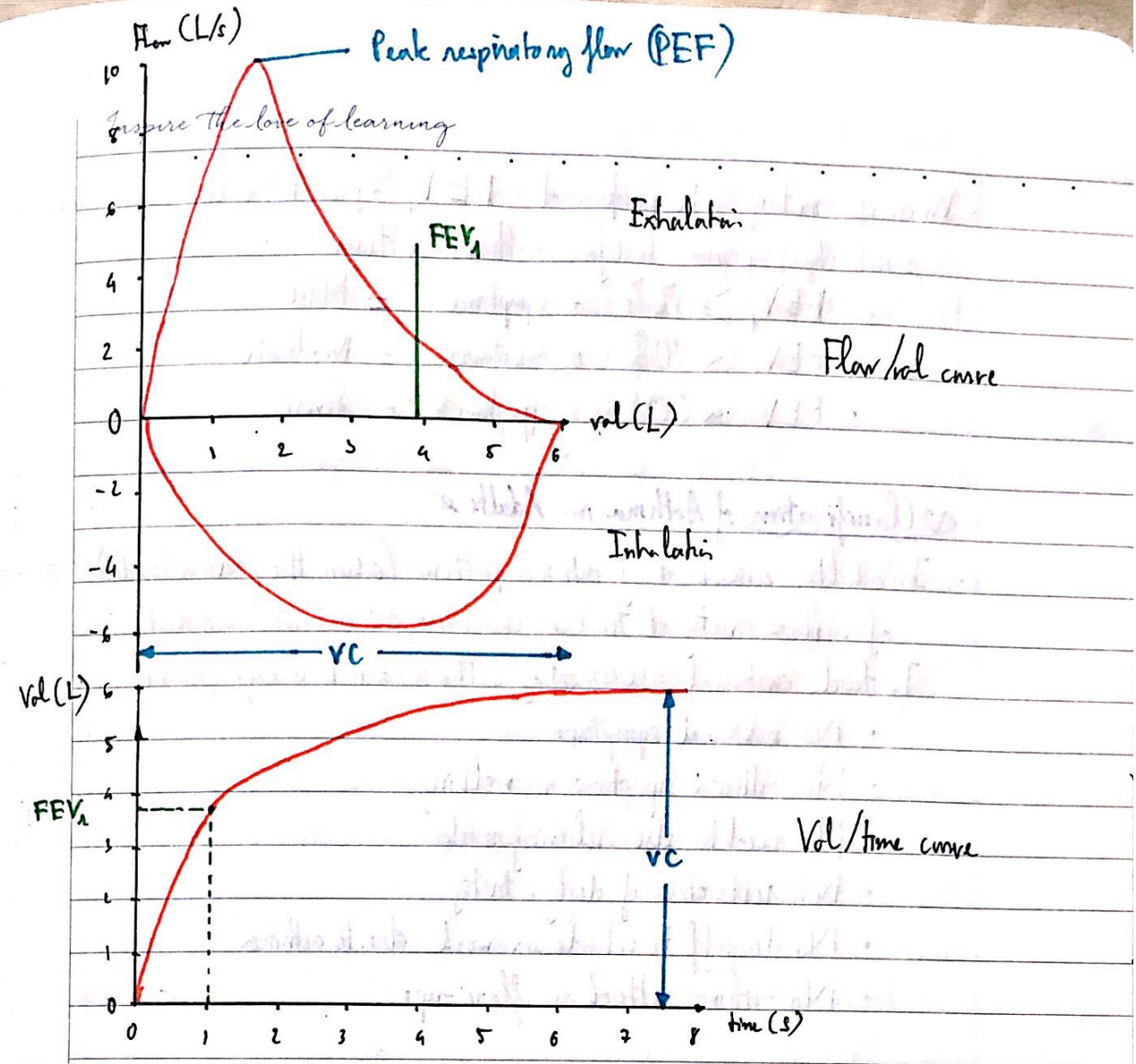

Assessment of asthma
~Classification

Infrequent intermittent asthma		Symptom-free for ≥ 6 weeks at a time (can have symptoms between flare-ups)
Frequent intermittent asthma		Flare-ups > 1 every 6 weeks but no symptoms between flare-ups
Persistent asthma	Mild	At least 1 of: • Daytime symptoms > 1 per week but not everyday • Nighttime symptom > 2 per month but not every week
	Moderate	Any of: • Daytime symptoms daily • Night time symptoms > 1 per week • Symptoms some times restrict activity or sleep
	Severe	Any of: • Daytime symptoms continual • Night-time symptoms frequent • Flare-ups frequent • Symptoms frequently restrict activity or sleep

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- When spirometry can be performed, FEV_1 % predicted will be used along w/ pt's & intensity of symptoms to define asthma patterns.
  - $FEV_1 \geq 80\%$ + symptoms = Mild
  - $FEV_1 < 80\%$ + symptoms = Moderate
  - $FEV < 60\%$ + symptoms = Severe

Classification of Asthma in Adults

- In adults, assessment of asthma pattern (as in the previous table) & the classification of asthma severity at time of diagnosis are not recommended.

Instead, continual assessment of asthma control is high priority

- No nocturnal symptoms
- No asthma symptoms on walking
- No need to use relieving meds
- No restriction of daily activity
- No days off to school or work due to asthma
- No asthma attack or flare-ups

Asthma severity assessment at the time of an acute event

- Acute management is based on assessing severity (mild/moderate; severe; life-threatening) while starting bronchodilator treatment immediately

Mild/moderate	• Can walk, speak 1 whole sentence in 1 breath • For young children, can move around, speak in phrases • O_2 saturation > 94%
Severe	Any of these: • Use of the accessory muscles of neck or intercostal muscles or "tracheal tug" during inspiration or subcostal recession (abdominal breathing) • Dyspnea → unable to finish 1 sentence / breath • Obvious respiratory distress • O_2 saturation 90-94%

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	• ↓ conciousness e collapse
	• Exhaustion
Life-threatening	Any of these: • Cyanosis (Bluish skin due to lack of O_2)
	• Poor respiratory effort, soft/absent breath sound
	• O_2 saturation < 90%

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II) Pharmacology of medications & management of acute & chronic asthma

Pharmacological approach to treating respiratory disorder (asthma)

Drug classes that can be used:

- Short-acting β_2-agonists (SABA) & long-acting β_2-agonists (LABA)
  - SABA: Salbutamol, Terbutaline
  - LABA: Salmeterol, Eformoterol (Formoterol)

- Inhaled corticosteroids (ICS) & oral/IV corticosteroid:
  - ICS: Beclomethasone, Budenoside, Ciclesonide, Fluticasone
  - Oral: Prednisolone, Methylprednisolone, Prednisone
  - IV: Hydrocortisone

- Leukotriene receptor agonists (LTRA)
  - Montelukast

- Mast cell stabilizer (Cromones)
  - Sodium cromoglycate, Nedocromil sodium,

- Muscarinic receptor antagonists short-acting (SAMA)
  - Ipatropium bromide

- Monoclonal eg. IL-5 antagonist; anti-IgE
  - IL-5 antagonist: Mepolizumab
  - Anti-IgE: Omalizumab

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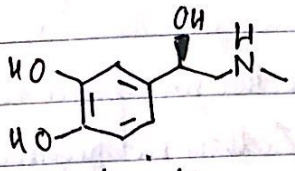
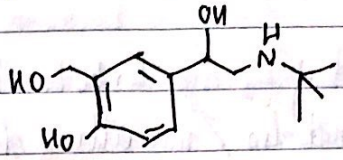
β_2 – adrenoceptor agonists

Mechanism:

- Mimic adrenaline, which is a mixed β & α agonist but w/ a slight selectivity to β & can be used to treat acute asthma attacks
  Salbutamol has better β_2 selectivity & was design to avoid metabolism by COMT

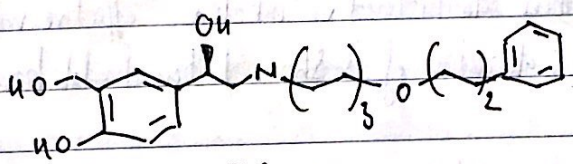


Adrenaline



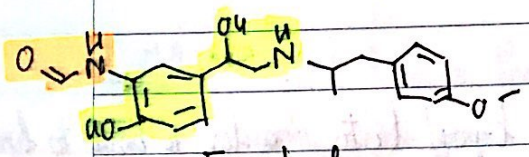
Salbutamol

From there, compounds were design to provide even better duration of action & selectivity
Eg: Salmeterol has longer duration

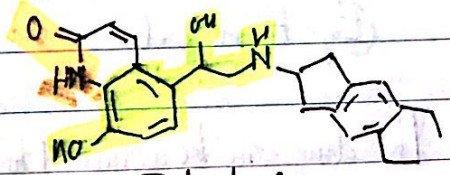


Salmeterol

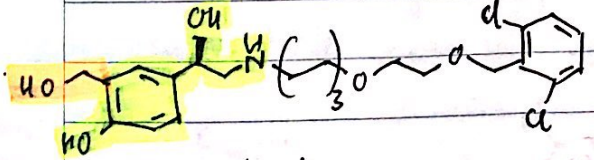
- The catechol groups are metabolized by COMT → inactivate & readily excreted.
  → The additional of a methylene group prevents the metabolism, as seen in many later drugs (could have variations)



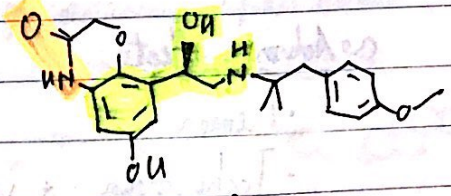
Formoterol



Indacaterol



Vilanterol



Olodaterol

- The activation of β_2-adrenoceptor activate the subunit α_s, which activates AC generating a high-cAMP environment. cAMP inhibits the MLCK, which prevents the smooth muscle contraction.

  In addition, cAMP also activate PKA, which phosphorylates the membrane Ca^{2+} channels and deactivates them → ↓ intracellular Ca^{2+}

- The effect of β_2 agonists will be observed no matter what bronchoconstrictor is present. β_2 agonists also ↗ mucociliary clearance via ↗ ciliary beat frequency, ↓ microvascular leakage & inhibit release of pro-inflammatory mediators from mast cells, basophil, eosinophil...

- SABAs are often administered via inhalers: effective within minutes, peak effect 30-90min, duration of 3-5h. Patient should have this prn (as needed)

- LABAs are usually not to be used as monotherapy for asthma. They are introduced as part of a step-up therapy, when good asthma control cannot be achieved by ICS alone. Effective 10-20min, max effect 2-4h, duration 8-12h

- Some LABAs can be used as a reliver.
  Eg: Formoterol

- The drug can be designed to increase lipophilicity in order to bind to lipid component → act as a depot for slow release

Adverse effects

- Tremor
- Tachycardia + vasodilation
- Cardiac arrhythmia
- Headache
- Nausea, vomiting, diarrhea

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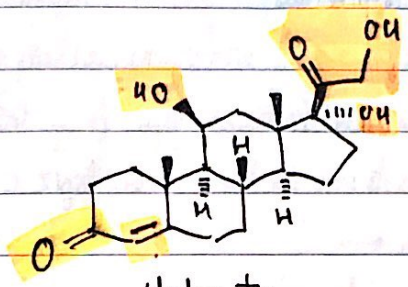
Glucocorticoids

- Glucocorticoids refer to any of the corticosteroid that involve in the metabolism of carbohydrates, proteins, fat & have anti-inflammatory activity

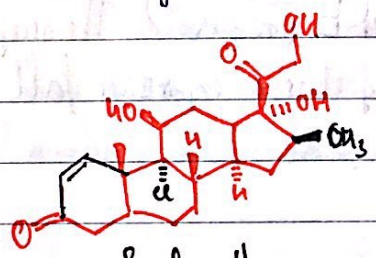
Hydrocortisone is one corticosteroid that can be used for anti-inflammation & other infections (eg anaphylaxis, anchenal insufficiency)

The highlighted functional groups below are important for binding to glucocorticoid receptors:

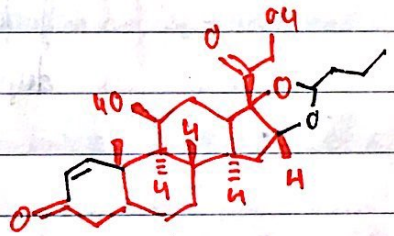


Hydrocortisone

Other drugs are built on this structure:

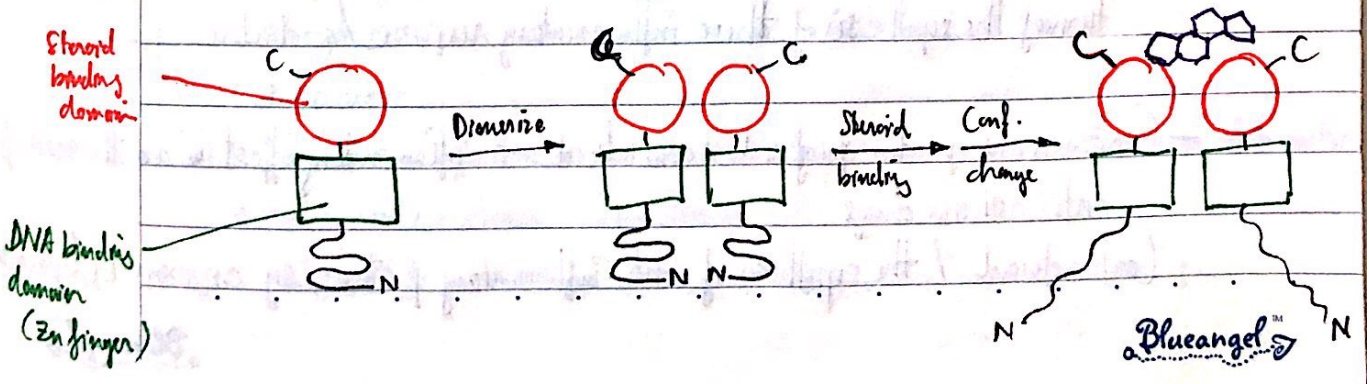


Beclomethasone



Budenoside

- Glucocorticoid traverse the cell membrane & bind w/ specific cytosolic glucocorticoid α (GR_α) receptors. Binding to dimerized GR_α receptor initiates a conformational change revealing the DNA binding domain, & the zinc fingers allows binding of the complex w/ the glucocorticoid response element (GRE) in the DNA



- The dimerized steroid - receptor complex then translocates into the nucleus where it attaches to the binding site (GRE)

Depending on the gene target, altering of mRNA may have different outcomes upregulation or down regulation.

- **Up-regulation:** The transcriptional mechinery is presumed to operate at low level. The binding of GR_α complex to the GRE in the promoter sequence act as transcription factor to increase mRNA synthesis

- **Down-regulation:** The transcriptional machinary is constitutively driven by transcription factors at the GRE ("negative"). The receptor complex displaces these factors & expression fall

- Gene activation results from the acetylation of nuclear histones around which DNA is wound, this opens the chromatin structure & allows gene transcription & synthesis of inflammatory proteins

Corticosteroid recruit histone deacetylase to activate genes, this reverses acetylation & turns off the synthesis of these inflammatory responses/mediators.

- Corticosteroid produce profound & generalized anti-inflammatory effect & are the most effective anti-asthma drugs

Corticosteroid ↑ the synthesis of anti-inflammatory proteins, eg annexin 1 (lipocortin)

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a protein that inhibits the production of arachidonic-derived mediator (PG, TX, LT, PAF)

Corticosteroid ↓ synthesis of pro-inflammatory proteins, eg Th2 cytokines, PG

- In summary, corticosteroids can:
  - ↓ Bronchial hyper-responsiveness, vascular permeability & mucus secretion
  - ↓ Lymphocyte, eosinophil, monocyte & basophil cell counts
  - Inhibit allergen-induce influx of eosinophils & ↓ mediators release from eosinophils & basophils
  - ↓ formation of cytokines involved in asthmatic inflammatory response (IL)
  - ↓ IL-3 synthesis (regulate mast cell production)
  - Inhibition induction of COX-2 → inhibit synthesis of PGE_2 & PGI_1
  - ↑ annexin-1 → inhibit formation of LTB_4, Cys LT, PAF & PG
  - ↓ production of IgE & IgG
  - Upregulate (or prevent down-regulation) of β_2-adrenoreceptor

- Examples of ICS: Budesonide, Beclomethasone, Fluticasone, Ciclesonide

ICS: as a preventer medication for persistent asthma. For poor-controlled asthmas, another LABA can be used.

Adverse effects

- Local side effect when using ICS:
  - Oropharyngeal candidiasis (Thrush)
  - Coughing
  - Dysphonia
  - Hoarseness

These local side effects can be minimized by rinsing mouth after each administration & use a spacer device when the inhaler device is an MDI (Label 14)

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- Systemic effects for oral corticosteroids
  - Adrenal suppression
  - Cataracts (cloudy lens)
  - Glaucoma
  - Growth suppression
  - Acne
  - Hirsutism (unwanted male-pattern hair growth in women)
  - Osteoporosis

Systemic corticosteroids have slower onset action (3h), max effect 9-12h & prolonged use is limited by these adverse effect.

Typically used as short course (5-10 days)

∞ Use of ICS in children

- Effectiveness of ICS on children depends on: age, triggers, wheezing phenotype, current exposure & genotype.

Overall, ICS seems to be more effective in older children & those w/ more severe symptoms

- Regular treatment w/ ICS improves wheezing, asthma symptoms & lung function & reduce flare-ups in infants & preschoolers w/ persistent wheezing or asthma

In schoolaged children w/ mild asthma, regular low dose of ICS treatment ↓ the rate of flare-ups that require treatment w/ oral corticosteroid, comp w/ no treatment & prn SABAs for wheezing episodes.

- Early introduction of ICS for children w/ recurrent wheeze doesn't prevent airway remodelling, improve long-term lung function or prevent the onset of persistent asthma

- ICS generally is considered safe in children, but the potential effect related to

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its regular use, especially in higher doses continue to be a matter of concern. ICS therapy should always aim to reach the lowest possible dose because most adverse effects are dose-dependent and are more common in individuals receiving concomitant oral or nasal corticosteroids.

The potential adverse effect of ICS need to be weighed against their benefits to control persistent asthma, especially that its safety profile is markedly better than oral glucocorticoids.

Mast cell stabilizers (cromones)

- Mast cell stabilizers reduce the immediate & delayed phases of the asthmatic response & ↓ hyperreactivity, However, this effect is weak & short-acting.

Cromoglycate & Nedocromil have been shown to:

- Inhibit IgE-mediated release of inflammatory mediators
- ↓ exaggerated responses following irritant receptor stimulation, suppress sensory C-fiber responses & desensitize neuronal reflex including vagal reflex
- ↓ the release of neuropeptides

- Both drugs are inhaled & use prophylactically as anti-inflammatory but not as bronchodilators
  → Not used for acute asthma

Unknown mechanism of action, but may be related to the inhibition of Ca^{2+} channel thus ↓ Ca^{2+} influx

- Although cromones are less effective than ICS in controlling asthma & lung function they can be given to:
  - Those who chose not to take ICS
  - Those who cannot tolerate ICS
  - Those whose symptoms limited to exercise-induced bronchoconstriction

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- Cromones must be taken multiple times per day, & the device requires daily maintenance due to the sticky formulation

Leukotriene receptor antagonists (LTRAs)

- LTs are separated in to LTB_4 & the cysteine LTs (C_4, D_4, E_4, F_4)
  They are very strong bronchoconstrictors (10000 times more effective than histamine)
  LTE_4 is less potent than E_4 & D_4, but longer-lasting

- LT antagonists relax smooth muscle, alleviating bronchoconstriction caused by the action of cysLT (which act on cys-LT1 receptor to ↑ intracellular Ca^{2+} & $G\alpha_q$ activation)

- Montelukast & zafirlukast are examples of LTRAs.
  They relax smooth muscle, ↓ airway hyper-responsiveness, ↓ leukocyte activation & eosinophilia, ↓ mucus secretion, ↓ microvascular permeability
  LTRAs are used as a preventer med in children or also in management of ~~exercise~~-induced asthma & as alternative preventer in adults (not 1st line)

- Montelukast is registered by the TGA for use in children ≥ 2yo
  Based on data, cannot define which children will benefit from the therapy.

The main role of montelukast:
- Alternative to low dose ICS in children w/ frequent-mild asthma

- Drawbacks:
  - In adults & adolescents w/ asthma that is not controlled by low dose ICS, LTRAs is less effective than LABA + oral steroids in reducing asthma flare-ups
  - Addition of LTRAs is associated w/ less lung improvement & quality of life than LABA
  - While LTRA ↓ sputum eosinophilia, no evidence for ↓ inflammation in general.

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- However, the oral route may be convenient.

- LTRAs are preventers & work best in mild asthma, thus a reliver (SABA) is still required.

- Montelukast is well tolerated, but some survey suggest association w/ psychiatric disorder in children

Inhaled muscarinic receptor antagonist (SAMA)(LAMA)

- Short-acting muscarinic receptor antagonists eg. Ipratropium & Tiotropium relax smooth muscle, relieve bronchoconstriction caused by overactive parasympathetic input.

- Inhaled Ipratropium (via a metered dose inhaler or mix w/ salbutamol in a nebuliser) is a 2nd line bronchodilator in the management of acute asthma, when salbutamol is not enough

- Tiotropium via mist inhaler can be an add-on option in adults who have severe asthma flare-ups within the previous year, despite maintenance treatment w/ ICS+LABA

Monoclonal antibodies

- This therapy is reserved for managing severe, high-risk, & difficult-to-control asthma in adults

Omalizumab is the only biologic specifically designed to block IgE
→ ↓ release of mediator in early phase & late phase in the allergic cascade
It should not be used for acute asthma exacerbation.

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- Omalizumab can be considered for adult & children ≥ 12yo, w/ moderate to se allergic asthma despite ICS treatment & raised IgE levels
Is given 150 - 300 mg subcutaneously (injection) every 2-4 week

- Anaphylaxis has been reported after omalizumab dosing (0.1-0.2%)
Other adverse effects:
- Arthalgia (8%)
- Pain (general) (7%)
- Leg pain (4%)
- Fatigue (3%)
- Dizziness (3%)
- Fracture (2%)
- Arm pain (2%)
- Pruritus (2%)
- Dermatitis (2%)
- Ear ache (2%)

In pediatric patient, some other adverse effects have been reported.
- Nasopharyngitis
- Headache
- Pyrexia
- Upper abdominal pain
- Pharyngitis streptococcal
- Otitis media
- Viral gastroenteritis

- Mepolizumab is an add-on for ≥ 12yo w/ severe refractory eosinophilic asth (asthma associated w/ a combination of severe asthma & eosinophilia)
Mepolizumab should not be used w/ acute asthma
Mepolizumab 100 mg is given by injection every 4 weeks
Mepolizumab binds to IL-5 & inhibit IL-5 signalling
→ ↓ production & survival of eosinophils (mechanism not yet confirmed)

- Adverse effect of Mepolizumab:
- Hypersensitivity reactions
- Headache
- Injection-site reaction
- Back pain
- Fatigue

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Administration of asthma meds

- Inhalation = primary route for both "preventers" & "relivers"
  → Large number of delivery devices are available, determined by the choice of drug

Patient should have the ability to use a device satisfactorily, assessed by a competent health professional

- Inhalation route is the mainstay of respiratory care due to these advantages:
  - Quick onset of action
  - ↓ total dose required compared to other route
  - Higher in situ drug concentration than oral/parenteral routes
  - Less systemic absorption → less systemic side effects

- The 4 main types of inhaler devices for asthma & COPD meds:
  - Manually-activated pressurized metered-dose inhalers (pMDI) (conventional)
  - Breath-activated pressurized metered-dose inhalers
  - Dry powder inhalers (DPI) (multidose & capsule types)
  - Mist inhaler

Correct techniques base on the device. Poor inhaler techniques → worse outcomes
Techniques worsens over time → Regular check for ensuring safety, including physical demonstration must be tested & trained.

- Some familiar devices:
  - Accuhaler
  - pMDI
  - pMDI + spacer
  - Turbuhaler.

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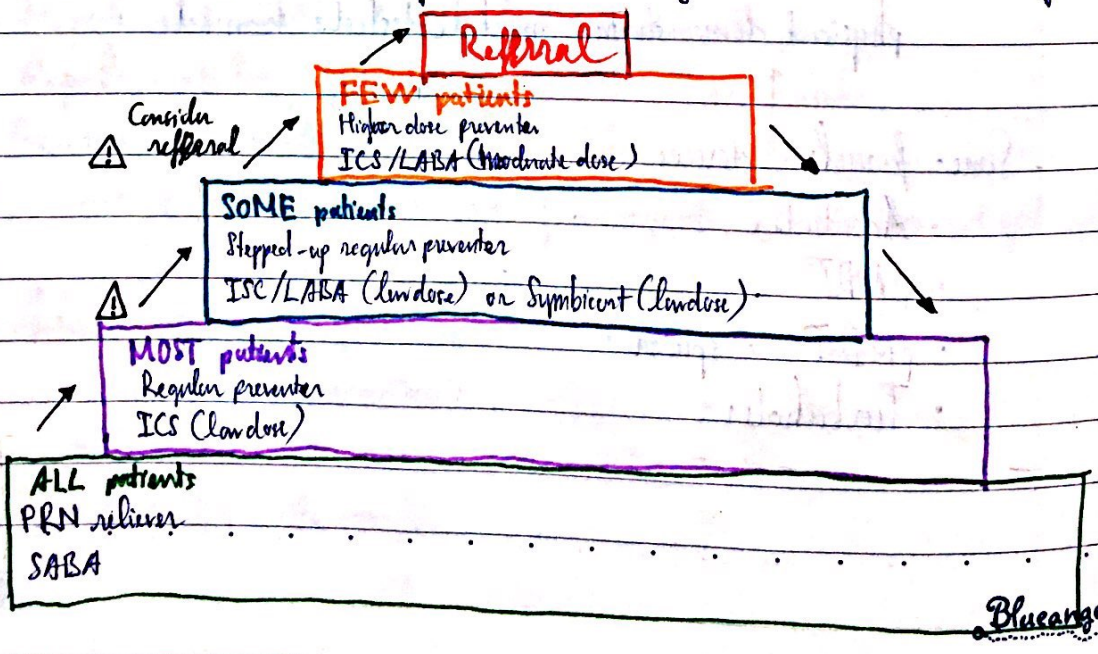
General principles of asthma management & drug treatment

General principles for adults:

- Aim for early control, w/ stepping up or down of treatment as required
- Before a new drug therapy
  - + Check compliance w/ existing therapy
  - + Check inhaler technique
  - + Eliminate trigger factors
- Prescribe reliever therapy for all patients w/ symtomatic asthma:
  - + Inhaled SABA is a standard therapy & should be carried by all patients (except those using budesonide - formeterol)
  - + Formoterol is an effective reliever, do not require a separate SABA
- If a "preventer" med is indicated, start w/ low-dose ICS. Once controlled, reduce ICS dose to lowest effective dose when asthma is consistently well-controlled
- Adults w/ moderate persistent asthma: addition of LABA
- If asthma is not adequately controlled, refer to a specialist

— The following budesonide - formeterol combination can be used in maintenance & reliever regimens: (Symbicort)

- DPI 100/6 mcg or 200/6 mcg
- pMDI 50/3 mcg or 100/3 mcg
- Neither 400/12 mcg or 200/6 mcg should be used this way



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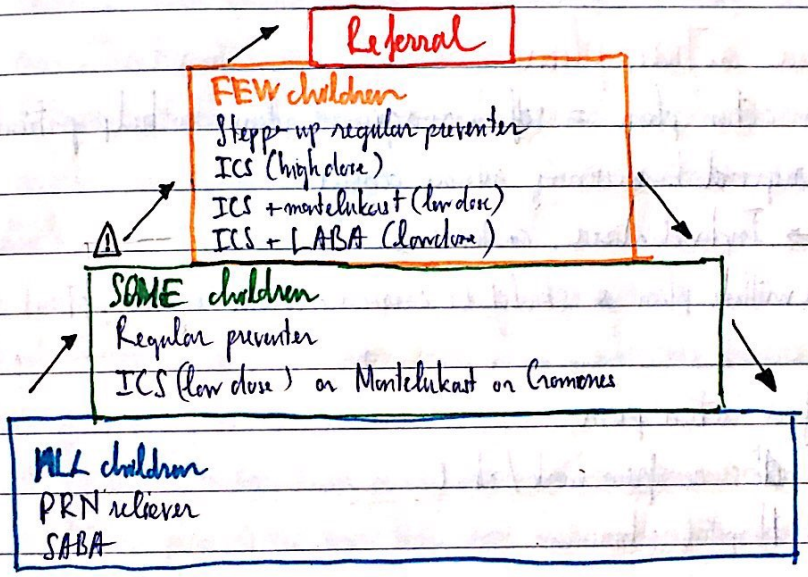
General principles for children:

- SABA should be prescribed as reliever therapy for all children w/ symptommatic asthma
- ICS > 250mcg of beclomethasone (or equivalent) should only be prescribed on specialist advice
- Limited evidence for the efficacy of LABAs in children, but can be used in combination w/ ICS when initial preventer is not effective
- Frequent intermittent-to-mild persistent asthma — low dose ICS or LTRAs or inhaled cromones
- Moderate to severe asthma — ICS is preferred, may consider adding montelukast or LABA (low dose) to the low dose ICS



- Start treatment w/ step most appropriate to severity & step up/down if needed.

Improvement should evident within 1 month

Review technique, compliance & avoidance risk before changing med dose

- Step up if not controlled
- Step down if well-controlled for 3 months

Goal: least meds to control

Review every 3-6 month when asthma is under control

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- The responsiveness are reduced if the cause of wheezing is due to respiratory infections & wheezy bronchitis (usually viral)

Many children from 2-5 w/ wheeze don't have asthma. Many have viral-wheeze associated w/ a respiratory infection or wheezy bronchitis

These children are well in the interval between episodes, are non-atopic & have good prospect of outgrowing the tendency to wheeze in later child hood

Standard approach: use SABAs as needed. ICS & oral steroids don't seem to be helpful, but LTRA may be useful as a long-term preventative agent & as an "episode modifier"

Asthma action plan

- Asthma action plan = self-management plan to help patient/carer to recognise & respond to worsening asthma control
  → Individualized, customized.

It is a written plan & should be carried around by the patient all the time

- Use of a action plan
  - ↓ absence from work/school
  - ↓ Hospital admission
  - ↓ emergency visit
  - ↓ reliever meds use
  - ↓ lung function

and should include:

- Usual meds for asthma & allergy
- Clear instruction on how to change meds
- When & how to get med care, including during emergency
- Name of person preparing the plan
- Date

Many plans follow traffic light system

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Green zone – doing good
Orange zone – getting worse
Red zone – medical alert

Pharmacists' role in asthma action plan

- Working w/ doctor to create a well-explaining plan so that patients can adjust their therapies according to their needs.

The plan is often based on an objective measure of lung function, eg PEF

For PEF measurement, it is better to take their personal best within them predicted value. Care should be taken if PEF falls. If no symptoms, could be over-treatment.

PEF measurement is not recommended for <12 yo. In most children w/ asthma, a change in symptoms is as effective as PEF for indicating the worsening of asthma

Patient preferences should also be considered.

- Patient should review the plan annually, & whenever there is any significant change

When reviewing, consider:

- Does the person know where their written plan is?
- If the plan is use more than once because of worsening asthma in the last 12 months review the person's need asthma treatment, adherance, technique, exposure to triggers
- Are listed meds & instruction current & appropriate?
- Are contact details for medical care & acute care updated?

Asthma emergency

- Any of these, should be taken to the emergency department (ED):

- Severe respiratory distress
- No immediate & sustained response to reliever
- Despite treatment, getting worse
- Asthma action plan suggests medical care
- PEF <60% of personal best after reliever

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Asthma 1st aid (4×4×4)

- Sit the person upright. Be calm & reassuring
- Give 4 puffs of reliever (preferably spacer)
- Use 1 puff at a time + 4 breaths after each puff
- Wait 4 mins, if nothing, use another 4 puffs
- No improvement, call 000
- Keep giving 4 puffs / 4 mins until ambulance arrives

(upto 6-8 puffs / 5 mins in adults)

Acute asthma management in the ED

Based on the National Asthma Council of Australia:

- Assess severity while starting SABA immediately
- Administer O_2 therapy to achieve 92-95% saturation (adults) or ≥ 95% (children)
- Start systemic corticosteroid within the 1st hour of treatment & continue for 5-10 day (oral unless dysphagia, then 100mg IV hydrocortisone /6h)
- Repeated reassessing response to treatment & either:
  - + Continue treatment or adding until resolved
  - + Transfer patient to intensive care unit
  - + Hospitalize the patient
- Observing the patient for at least 1h after dyspnea has resolved, providing post-acute care & arranging follow-up

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Week 3 12/3/2018

I) Pathophysiology, case finding, diagnosis & classification of COPD

Overview

- COPD is characterized by airflow limitation that is not fully reversible. However, it can be prevented & treatable.

The airflow limitation is usually progressive & associated w/ an abnormal inflammatory response of the lung to noxious particles or gases.

- COPD encompasses a number of diseases :
  - Emphysema (Pink puffer) : The alveoli are affected ; the loss of elastin in the alveoli results in ↓ surface area & collapsed alveoli
  - Chronic bronchitis (Blue bloater) : Smooth muscle hypertrophy & contraction, & mucous hypersecretion

- Common symptoms :
  - Dyspnea, change in respiratory rate & the effort in breathing
  - Chesty chronic cough
  - Excessive sputum production
  - Weakness, fatigue, exercise intolerance
- Risk factors :
  - Cigarette
  - Air pollutant
  - Genetic
  - Recurrent infection
  - Low eco status
  - α_1 antitrypsin deficiency
- COPD is heterogenous, slowly progressive disease, w/ multiple clinical features & comorbidities, requiring management to be tailored to the individual
  → Challenging

Spirometry is the gold standard for COPD diagnosis

Variety of pharmaco & non-pharmaco treatments are used in a stepwise fashion to control symptoms & ↓ COPD exacerbation

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- Like asthma, a COPD action plan serves to help patients & carers recognise & respond to signs of an exacerbation to prevent hospitalization

COPD-X plan:

- Confirm diagnosis
- Optimize function
- Prevent deterioration
- Develop a plan of care
- Manage exacerbation

Pathophysiology

- Similar to asthma, COPD is an example of an obstructive respiratory disorder, but w/ some major differences. As mentioned, COPD alters the conduction of air from the environment to the alveoli by 2 main mechanisms:
  - Smooth muscle hypertrophy & excess production of mucus
  - Tissue damage & alveolar degradation

- In contrast to asthma, COPD is largely irreversible, & one distinction from asthma is the observed inflammatory profile in COPD

- Unlike asthma (symptoms may vary day to day), symptoms of COPD are relatively consistent

COPD exacerbation

- Characterized by ↑ dyspnea, cough & sputum, is acute in onset & typically warrant a change in meds or hospital admission

Patients w/ more severe COPD (as suggested from spirometry) are more likely to suffer 12-month mortality rate following hospital admission is about 25%

→ Better to prevent rather than hospitalization

- Triggers for exacerbation include viral & bacterial infection, heart failure, psychosocial stressors & air pollutants

Pathophysiology of COPD (detailed)

Inflammation & cellular changes in COPD

- The inflammation observed in the respiratory tract of COPD patients appears to be a modification of the normal inflammatory response of the respiratory tract to chronic irritants eg. cigarette smoke

Chronic inhalation leads to chronic inflammation, & in COPD there is an influx & activation of:

- Macrophages
- Neutrophils
- Lymphocytes
- Eosinophils, especially when there is clinical overlap w/ asthma

All these cells, together w/ epithelial cells & other structural cells release multiple inflammatory mediators, eg IL (IL-8, IL-1b, IL-6), TNF-α & nitric oxide, LTB_4 & reactive oxygen species

Neutrophils also release other destructive peroxidases & elastases.

⟶ Effects: Mucus hypersecretion, Fibrosis, Alveolar wall destruction

- The inflammatory profile is distinctive from asthma
  - Asthma: ↑IL-4 & eosinophils
  - COPD: ↑IL-8 & neutrophils

Despite differences, both condition may overlap & it is recognized that eosinophil & neutrophils can release mediator that can destroy lung function:

- Chemotactic factors: attract inflammatory cells
- Proinflammatory cytokines: amplify the inflammation process
- Growth factors: induce structural change

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- Oxidative stress & excess proteinases in the lung are likely to further modify inflammation ⟶ changes in pathology

The inflammation tends to persist even after smoking cessation, thru unknown mechanisms
- Oxidants from cigarett smoke
- Release from inflammatory cells
- Antioxidant reduction
- Oxidative stress

- Mucus hypersecretion ⟶ chronic productive cough, a clinical feature of bronchitis & may not necessarily be associated w/ airflow limitation

Mucus hypersecretion is due to hyperplasic & hypertrophic changes:
- ↗ number of goblet cells } result from irritation & noxious gases
- Enlarged, dilated submucosal glands
- Inflammatory mediators & proteases release via the activation of EGF receptors

These excess mucus are difficult to remove via coughing only, & mucus is a good bacterial growth medium ⟶ frequent bacterial chest infection

Effects – Symptoms

- Patient w/ COPD will have a ↓ inspiratory & expiratory flow – ↓ fresh O_2 air reaching the alveoli

- The extent of inflammation, fibrosis & secretions correlates w/ reduction in FEV_1 & FEV_1/FVC ratio

The peripheral airway limitation progressively traps gas during expiration, leading to hyperinflation
⟶ ↓ inspiratory capacity at rest, & is commonly associated w/ exertional dyspnea & limited exercise capacity

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- Observed symptoms:
  - Hyperinflation & gas trapping
  - Impaired gas exchange due to damage to the respiratory membrane (type I alveolar cells & capillary endothelial cell due to proteinases)
  - Ventilation : perfusion (V:P) mismatch (efficient supply/removal of air is not matched by an adequate blood supply or vice versa)
  - ↑ breathing effort
  - ↓ ventilation drive, ventilatory muscle impairment
  - ↑ dead space ventilation

The net effect of gas exchange abnormality → hypoxemia (low O_2) & hypercapnia (high CO_2).

- During exacerbation of COPD: ↑ hyperinflation & gas trapping, w/ ↓ expiratory flow → ↑ dyspnea
Also worsening hypoxemia
Other condition eg. pneumonia, thromboembolism, cardiac failure may mimic or aggravate an exacerbation of COPD

- Repeated cycles of inflammation, bacterial infection then inflammation again cause thickening & narrowing of the airway
  → Permanent damage & remodelling
When exhalation is affected, the alveoli then become overinflated & push against the diaphragm, preventing efficient mvt of the diaphragm - the diaphragm is unable to form the optimal concave shape for breathing
  → Much more effort

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Comparision w/ asthma

- COPD & asthma are associated w/ chronic inflammation of the RT, w/ differences in inflammatory cells & mediators involved in the 2 diseases
Some patients w/ COPD have features consistent w/ asthma & may have mixed inflammatory pattern w/ ↑ eosinophils

	Asthma	COPD
Onset	Early in life (<30 typically)	In mid-life (>40)
Family history	Common	Uncommon
History of atopy	Usual (w/ allergic rhinitis & eczema)	Uncommon
Cause	• Atopy (Allergy & immunology) • Non-atopy	• Irritants, noxious gases • Genetic (rare)
Site of inflammation	Mainly larger airways	Mainly smaller airway & lung parenchyma
Inflammatory mediators	Eosinophils, $CD4^+$ T cells, T_h2 cells	Neutrophils, $CD8^+$ T cells, T_c cells
Cough	Non-productive, nocturnal, post exercise	Productive, early morning
Dyspnea	Episodic	Persistent
Nocturnal symptoms	Common	Uncommon
Purulent sputum	Uncommon	Typical
Chest auscultation	Wheezing during flare-ups	↓ breath sound
Reversibility on dilator	Almost fully reversible	Partial to none
Response to ICS	Good	Limited

Diagnosis for COPD

- A questionaire is used under the form of check list (yes-no) to screen for risk & whether a patient needs to take a spirometry test.

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Do you:
- have a new, persistent or changed cough?
- cough up mucus, phlegm or blood?
- get breathless more easily than others in your age?
- experience chest tightness or wheeze?
- have frequent chest infections?
- experience chest pain, fatigue or sudden weight loss?

If you answered yes to any questions, your lung health could be at risk if you:
- smoke or have ever smoked?
- work in an environment that exposed you to dust, gas or fumes?

- The risk assessment checklist indicates the needs to have a spirometry test. Associated w/ the checklist is a microspirometry test
- test result w/ $FEV_1/FEV_6 < 0.75$ indicates that the patient has a high probability (86-90%) of abnormal lung function & a full spirometry must be undertaken. Other investigation may involve x-ray, hematology, biochemistry, complex lung function tests, exercise stress testing, ECG & echocardiography

Criteria:
- COPD is confirmed by the presence of persistent airflow limitation ($FEV_1/FVC < 0.7$)
- An FEV_1 increase >12% & 200mL constitutes a positive bronchodilator response, suggestive of reversibility
- If FEV_1 increase >400mL following bronchodilator, consider asthma or coexisting asthma/COPD

Severity	Post-bronchodilator FEV_1/FVC	FEV_1 % predicted
Mild	≤ 0.7	60-80
Moderate	≤ 0.7	40-60
Severe	≤ 0.7	<40

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* FEV_1 predicted: FEV_1 % of the patient devided by the average FEV_1 % in the population for every person of similar age, sex & body composition

II) Management of COPD

Role of the pharmacists

~ COPD-X Guidelines

- COPD-X highlights the evidence for key clinical recommendations in the diagnosis & management of COPD

Optimal COPD management relies on choosing appropriate meds & non-pharmacological measures w/ ongoing monitoring & titration of therapy

→ Multidisciplinary approach involves many health care professionals

~ Challenges

- Under-recognition & under-diagnosis of COPD → delay in initial treatment

COPD is also complicated, associated w/ various diseases eg. cardiovasc, anxiety, depression → add to the complexity

- Combination therapy has been demonstrated to be beneficial in patient w/ more severe COPD

- In a progressive disease eg COPD, more pharmacological & non-pharmacological therapies are required to manage symptoms as time goes on

→ Utterly complicated med regimen for patients to manage

- Pharmacists can assist by identifying patient w/ characteristic COPD symptom to refer to a GP for spirometry. Smoking should be screened & assessed. Inplace pharmacist can help monitoring the treatment & adherence

~ Support Patients to Quitting smoking

- Tobacco = risk factor for COPD → Smoking cessation is a management

Health pro can motivate quit attempt & maintain long-term cessation

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- 5A's strategy for smoke quitting:
  - Ask & identify smokers at visit
  - Assess nicotine dependency & motivate to quit
  - Advice about the risk of smoking & benefits of quitting
  - Assist cessation
  - Arrange follow-up

- Nicotine dependent can be treated w NRT, varenicline & bupropion.
  Longer course may ↓ relapse

Refer to the self made note about smoking cessation

Strategies for COPD management

Non-pharmacological strategies for COPD

- Pulmonary rehab that involves programs devised by a physiotherapist that allow exercise training alone or in conjunction w/ patient education or other non-pharmacological intervention & psychological support
  This method is evident in patients w/ stable COPD & post-exacerbation of COPD
  Exercise should be encourage as inactivity may result in COPD exacerbations

Pharmacological strategies for COPD

- Aim to ↓ symptoms, prevent exacerbations & improve health status by targeting the pathophysiology of COPD
  None of existing medications for COPD modify the long term decline of lung function
  Choice of therapy depends on the availability, cost of meds, favorable response/side effect balance
  → Stepwise approach until well-controlled

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- The primary route for administration of meds for COPD is inhalation
  - → Required inhaling technique
    50%-100% of patients demonstrates wrong technique
  - → Worse outcome

The more inhaler devices & doses → more errors in inhaler use
→ The needs to optimize the n° of inhalers & doses

	Mild	Moderate	Severe
Typical symptoms	• Few symptoms • Breathless on moderate exertion • Recurrent chest infection • Little or no effect on daily activity	• Breathless walking on level ground • ↗ Limitation of daily activity • Cough & sputum production • Exacerbation requires Oral CS/ antibiotics	• Breathless on minimal exertion • Daily activity ↓ • Regular sputum production • Chronic cough • ↗ frequency & severity
Typical lung function	FEV_1 = 60-80% predicted	FEV_1 = 40-59% predicted	FEV_1 < 40% predicted

Non-pharma

RISK REDUCTION check smoking, support cessation, annual flu vaccine & pneumococcal vaccine

OPTIMIZE FUNCTION Encourage exercise, provide education, develop plans

CONSIDER CO-MORBIDITIES especially cardiovas diseases, anxiety, depression, lung cancer, osteoporosis

REFER to pulmonary rehab for symptomatic patients

Consider O_2 therapy, surgery, bronchoscopic intervention, palliative care service & advance care planning

Pharma

Start w/ short acting reliever (PRN)
SABA or SAMA

Add long-acting bronchodilator
LAMA or LABA
Review need for LAMA/LABA as a fixed-dose combination inhaler

Consider adding an anti-inflammatory
ICS/LABA and LAMA

Check device usage technique & adherence teach use

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Figure explanation:

- Some further therapies can be added when a patient transitioning thru the disease severity due to the progressive nature of COPD

Goal:

- Alleviate the symptoms
- Prevent COPD exacerbation

- The starting point for mild COPD is to commence a short acting reliever (SABA or SAMA)

If the patient has ongoing breathlessness or is experiencing COPD exacerbation, an additional LAMA or LABA should be done

LAMA & LABA can be used in combination to assist COPD management

As COPD progresses into the moderate & severe category, ICS should be considered (in the form of a combined ICS/LABA inhaler)

- Some therapies can be used as a combination, while others cannot.

	Drugs	SABA	SAMA	LAMA	LABA	LABA/LAMA	ICS/LABA
SABA	Salbutamol; Terbutaline		Yes	Yes	Yes	Yes	Yes
SAMA	Ipratropium	Yes			Yes		Yes
LAMA	Tiotropium, Glycopyrronium, Aclidinium, Umeclidinium	Yes			Yes		Yes
LABA	Salmeterol, Formoterol, Indacterol	Yes	Yes	Yes			
LABA/LAMA	• Indacterol/Glycopyrronium • Umeclidinium/Vilanterol • Tiotropium/Olodaterol • Aclindinium/Formoterol	Yes					
ICS/LABA	• Fluticasone/Salmeterol • Budesonide/Formoterol • Futicasone/Vilanterol	Yes	Yes	Yes			

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Pharmacological Strategies -

∞ Vaccination

- Inactivated influenza vaccine ↓ exacerbation due to flu in COPD, especially in epidemic years
  Adverse effect: mild, local, transient, self-limiting
- There is no increase in exacerbation before immunity has developed, but the patients are encourage to get the vaccine ASAP
  Annual vaccination is cost effective, particularly in patient w/ severe COPD

- >50yo who had immunisation w/ polysaccharide pneumococcal vaccine, plus 5year revaccinate will have protection against pneumonia & COPD exacerbations.
  Influenza vaccine has additive beneficial effect

∞ Bronchodilator

- Bronchodilators ↑FEV1 & change other spirometry variables
  Act by altering airway smooth muscle tone to ↗ airflow & tend to ↓ hyperinflation at rest

- Most often given: LAMA, LABA, ICS on regular basis to prevent or reduce symptoms
  Toxicity & side-effects are dose-related.
  SABA & SAMA are use PRN for symptom relief, but long-term use is not recommend
  If short acting bronchodilator is insufficient, long acting bronchodilator should be considered

- Formoterol & Salmeterol are twice daily LABA that significantly ↑FEV1, lung vol, dyspnea, health status, exacerbation rate & hospitalization, but show no effect on mortality or rate of decline of lung function

Idacaterol may produce coughing as side effect

Olodaterol & Vilanterol are additional once daily LABA that improve lung function & symptom

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~ Muscarinic antagonist

- The parasympathetic neurons innervate the bronchi & bronchioles, affecting airway smooth muscle, glands & vascular smooth muscle
  - M_1 : on post-ganglionic neurons' cell body, facilitating AChN neurotransmission
    on mucus gland to regulate secretion
    may be also on alveolar wall
  - M_2 : on post-ganglionic neurons' axon terminal as an inhibitory auto receptor
    on smooth muscle, inhibiting β_2-adrenoceptor signalling
  - M_3 : on bronchiole smooth muscle & mediate contraction via G_q & G_i
    on glands & mediate secretion
    on airway epithelium & ↑ cilliia beating & mucociliary clearance
    on tracheobronchial vasculature & mediate vasodilation

- Muscarinic antagonists relax smooth muscle caused by overactive parasympathetic input, also inhibit vasodilation to ↓ mucus secretion
  However, the drying of the mucus may result in the high viscosity of the liquid, thus hard to be cleared → prone to infection

- Target receptor M_3 : SAMA ; may also block M_2 to reduce bronchoconstriction via vagal nerve

  LAMA have prolonged binding to M_3, w/ faster dissociation from M_2

- Ipratropium & Tiotropium are designed to have minimal side effects
- Inhaled muscarinics are poorly absorbed → low systemic effect
  Extensive use of this class in wide range of doses has shown to be very safe
  Adverse effects: dry mouth, metallic taste

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∞ Anti-inflammatory agents

- An ICS / LABA combination may be considered in severe COPD (FEV_1 < 50% pred). However, additional ICS may ↑ the risk of pneumonia

Although LAMA/LABA appears to be more beneficial than ICS/LABA, the use of ICS/LABA remains an option for moderate COPD who need additional treatment

- Opposite to asthma:
  - Asthma: ICS first line, then LABA
  - COPD: LAMA/LABA first line, then ICS

∞ Mucolytic

- Mucolytic eg N-acetylcysteine (NAC), ambroxol, sobrerol & carbogsteine can have multiple action including:
  - ↓ sputum viscosity
  - Antioxidant
  - Antiinflammatory
  - Antibacterial

In patients w/ COPD, high dose (≥ 1200mg/d) NAC should be considered effective for ↓ exacerbation

Management of COPD

∞ COPD exacerbation - Prevention & Management

- COPD exacerbation: ↑ in dyspnea, cough, sputum, acute onset, typically warrant a change for medication or hospital admission

Trigger for exacerbation:
- Viral / bacterial infection
- Left ventricle failure
- Psychological stressor
- Pollution

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- Early recognition & management of exacerbations ↑ recovery & quality of life
COPD action plan serves to help patients & carers to recognize & respond to early signs:
  - Marked ↑ in intensity of symptoms
  - Patients then exacerbation characterized by ↑ dyspnea, cough, sputum plus one or more:
    + Lack response to appropriate community-based management
    + Inability to walk between rooms
    + Inability to eat or sleep due to dyspnea
    + Cannot manage at home even w/ home care resource
    + High risk comorbid conditions
    + Altered mental status, suggestive of hypercapnia
    + Worse hypoxemia or cor pulmonale
    + Newly occurring arrhythmia
    + Newly occurring hypoxemia ($CpO_2 < 92\%$)

- In hospital management of acute exacerbation
  - ↑ dose of salbutamol, 4-8 puffs via MDI/spacer every 3-4h
  - Morning dose of oral prednisolone 30-50mg for 5 days (IV shows no difference)
  - If associated w/ infection, oral amoxicillin or doxycyclin for 5 days
    If pneumonia is suspected → chest x-ray & treatment for pneumonia

∞ Self-management

- Self-management support is the systematic provision of education & supportive intervention by health care staff to ↑ patient's skills & confidence in controlling the problem
Including:
  - Emotional support
  - Problem solving
  - Decision making
  - Development of therapeutic partnership
  - Goal setting
  - Action planning

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Advanced stages of COPD

- In advanced stages of COPD, O_2 therapy may be used
Low dose morphine can also be employed to treat refractory breathlessness

- Patients in these stages experience many distressing symptoms :
  - Breathlessness
  - Fatigue
  - Depression
  - Anxiety
  - Insomnia

  } Palliative care (end of life care) to improve life quality

Early access to palliative care is recommended for patient w/ COPD & persisting symptoms
Active treatment may require a multidisciplinary team

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WEEK 6 19/3/2018

I) Pathophysiology of GORD

Patho physiology

∾ Normal swallowing

3 phases : Oral phase → pharyngeal phase → Esophageal phase

The voluntary reflex of chewing & mastication initiate the involuntary swallowing effect of the pharyngeal & esophageal phase

- Oral phase : conscious effort of ingesting food (chewing & mastication)
  swallowing begins when tongue push the bolus back against the soft palate
  the soft palate elevate to make way for food.

- Pharyngeal phase: food entering pharynx activate the swallowing center in the brainstem via touch receptor & sensory neuron
  the swallowing center signal the motor nuclei on the cranial nerves to initiate several events: ↑ Epiglottis closes the larynx
  Respiration stops
  Upper esophageal sphincter (UOP) opens

- Esophageal phase: transport food via the esophagus into the stomach
  esophageal peristalsis is a vago-vagal reflex involving sensory & motor neurons of the vagus nerves, initiate via ACh release, vasoactive intestinal peptide (VIP) or nitric oxide (NO) from the motor neuron
  the bolus reaches the lower esophagus causes the release of NO & VIP, leading to the relaxations of the lower esophageal sphincter (LOS) & initiate

* In this note, "GORD symptoms" term is referring to Gastro-esophageal reflux symptom, not the Gastroesophageal reflux disease. Blueangel

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Swallow disorder & GORD

- Occurs when the LOS relaxes w/o the associated peristaltic contraction
  → Transient LOS relaxation
  → GORD

Cause & Risk factor of GORD

Failure of LOS to close properly can be due to:
- The use of smooth muscle relaxant
- Weakened LOS (Unclear mechanism)

Factor	Known underlying mechanism
Overweight	↑ pressure on the stomach & weakening of LOS
High fat, sugar, salt diet	Prolonged gastric emptying time
Smoke, alcohol, coffee	Relax the LOS
Pregnancy	Changes in hormone lvls → slow digestive system & ↑ pressure on stomach
Gastroparesis	Prolonged gastric emptying time
Smooth muscle relaxant	Nitrates, Ca^{2+} blocker, β_2 agonist
Male gender	
Older age	
Caucasian ethnicity	
Family history	
Hiatus hernia	This occurs when there is a portion of the stomach protruding thru the hiatal ring in the diaphragm going into the chest cavity & can ↑ risk of developing severity of GORD
Zollinger Ellison Syndrome	↑ gastric production, ↑ gastric activity & worsen symptoms
Hypercalcemia	↑ gastric production
Scleroderma & Systemic sclerosis	Can be associated w/ esophageal dysmotility

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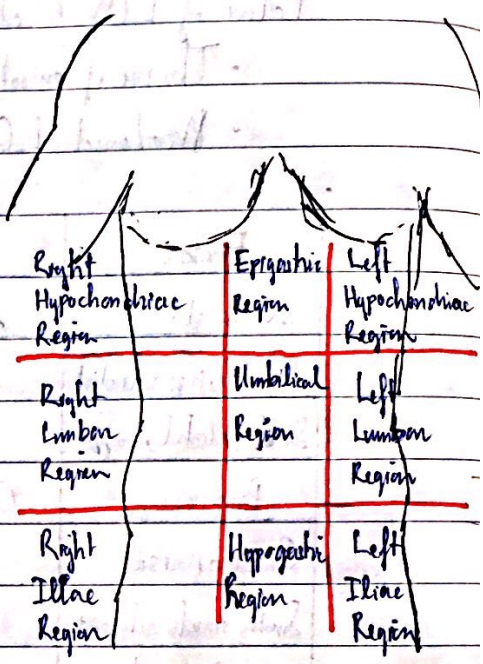
∾ Symptoms

- : heartburn, regurgitation, waterbrash
- Use LINDOCARF protocol to elaborate the symptoms

LINDOCARF

∾ Location

- Typically in the stomach region (epigastric) or the lower chest towards the neck
- App. 60% will also have upper ab pain/discomfort
- Atypical symptom can be non-specific & may indicate this is not GORD, or there are other condition occur simultaneously:
  - In the chest as chest pain (heart prob)
  - Waterbrash, metallic/sour taste (acid)
  - Voice changes/hoarseness (acid destroy larynx)
  - Asthma (GORD can trigger asthma symptoms)
  - Dry cough
  - Belching
  - Nausea
  - A lump in throat, or nocturnal choking



∾ Intensity

- GORD pain can be mild (0-3) to severe (8-10)
- GORD severity is not assessed by pain, but by the presence of atypical symptoms
  → Severe disease & complicated reflux → Refer

∾ Nature

- Clarify what "heartburn" & "regurgitation" as patients may not understand the terms
- Patients can also talk about chest pain, nausea, excessive salivation, pain on swallow, ...

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Duration
- Symptoms can occur over a minute, but typically over an hour

Onset
- Typically after meal or bending or laying down

Concomitant factors
- Refer to atypical symptoms
- About 40% of patients w/ irritable bowel syndrom (IBS) complain of reflux symptoms

Aggravating factors
- Large meal, w/ high fat/sugar/spicy
- Bending, laying down, straining
- More on table of trigger factors

Relieving
- PPIs, H_2 antagonists, antacids

Frequency
- Clinically significant impairment of wellbeing usually occurs when symptoms >2/week.

Red flag
- Redflags are alert signs/symptoms that can indicate a more serious underlying pathophysiology & require referral for further investigation

Referral symptoms
- Any of: Significant weight loss, recurrent vomiting, dysphagia, odynophagia, epigastric mass, cardiac chest pain, evidence of abdominal blood loss eg. hematemesis, melena, iron deficiency, anemia
- Daily symptom
- Age >55 or <18
- PPI is not helpful in 2 weeks
- Family history of cancer
- Long term NSAID therapy

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- If GORD is left untreated, can lead to
  - Peptic ulcer
  - Bleeding
  - Strictures / narrowing
  - Barrett's esophagus, if left untreated can develop into esophageal cancer

Identifying & Diagnosis of GORD

- It is important to note that a patient may experience GORD symptoms once a week, however this is considered to be normal
  → Can use medicine but not a diagnosis of GORD (symptoms ≠ disease)

- An initial diagnosis of GORD can be made knowing the presence of clinical sympto (using LINDOCARF) eg. frequency, location w/ risk factors
  Further investigation is needed if medication is not helpful or any "red flag" symp
  → Diagnostic methods that can be used:

Method	Definition	When to use	Implication
Gastroscopy	- Endoscopic procedure to examine the upper GI tract. Usually performed under anesthetic using a thin flexible tube w/ camera - Note: in more complex cases, other investigations may be required	- Any referral symptoms - Persistent despite adequate PPI - Screening for Barrett's esophagus in risk patients - Before & after surgical intervention of GORD - Dilating esophageal structure	- To look for complications eg. peptic ulcer, Barrett's & exclude other diagnoses - Signs of GORD can be seen visually but biopsies should be taken
H. pylori detection	- Breath test or biopsies during endoscopy	- If suspicious of peptic ulcers	- H. pylori doesn't cause GORD & can be protective against GORD, Barrett & esophageal carcinoma - Treating HP will not improve GORD symptoms

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Method	Definition	When to use	Implication
Barium swallow	- $BaSO_4$ is a metallic compound that can be shown up on X ray to detect abnormalities in the GI tract	- When symptoms are brought on by positioning or abdominal pressure. This is neither sensitive nor specific for GORD - In patient w/ dysphagia, this is not recommended for routine GORD diagnosis	- Can demonstrate complications of GORD eg. hernias or strictures - May be able to demonstrate inadequate gastric emptying

Management options

- Treatment depends on frequency, severity & types of symptoms
- For most patients, goal is to relieve the symptoms
  In patient with ↓ wellbeings, additional treatment is required to improve quality of life

∽ Mild intermittent GORD symptoms (≤1 episode /week)

- Diet & lifestyle modification:
  - Review when symptoms arise (LIFDOCARF)
  - Modify lifestyle according to symptoms & patients
  - Avoid food that can commonly induce GORD symptom + assess effectiveness (stop if not helpful)
  - Weight loss for overweight
  - Other: + Eat small meals
    + Drink between meals, not during
    + Avoid laying down after eating
    + Elevate bed head (if nocturnal symptoms)
    + Stop alcohol & smoke

Diet & lifestyle changes should be employed regardless severity

- Medication therapies can be added if lifestyle changes are insufficient:
  - Antacid (first line): $Mg(OH)_2$, $Al(OH)_3$
  - H_2-antagonist: Ranitidine, Cimetidine
  - PPI: Omeprazol, Esomeprazole

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- Antacid doses:
  - Antacid + alginate preparation: 10-20 mL oral prn
  - Antacid Mg + Al : 10-20 mL oral prn

- H_2 antagonist doses
  - Famotidine: 20mg oral, 1-2 times/day prn
  - Nizatidine: 150 mg oral, 1-2 times/day prn
  - Ranitidine: 150 mg oral, 1-2 times/day prn

∞ Frequent GORD symptoms (≥ 2 episodes/week) or ↓ quality of life

- Patients w/ GORD (not GORD symptoms) often need regular drug therapy in addition to diet & lifestyle changes
- PPIs are generally preferred to H_2 antagonists for initial treatment of GORD due to their effectiveness at standard doses

The response to PPIs also confirms the diagnosis of GORD in patients w/ no red flags.

- PPI doses: (standard):
  - Esomeprazole: 20 mg once daily
  - Omeprazole: 20 mg once daily
  - Rabeprazole: 20 mg once daily
  - Lansoprazole: 30 mg once daily
  - Pantoprazole: 40 mg once daily

- If a PPI is required, it should be trialled for 4-8 weeks. If the patient doesn't improve → ↑dose if no non-adherence or refer to GP

Once symptoms is controlled for 4-8 weeks, may commence step down of GORD therapy including:
  - ↓dose of PPI
  - Change to PPI prn
  - Trial of ceasing therapy

Planned

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If stepdown therapy cannot control symptoms, patient must resume the lowest effective dose & frequency of PPI to allow relief of symptoms

- There are groups of patients that will require ongoing treatment courses, including those w/:
  - Severe erosive esophagitis
  - Scleroderma esophagus
  - Barrett's esophagus.

- Schematic diagram for GORD treatment:

Therapy for mild intermittent symptoms
- Lifestyle changes may be adequate
- Meds: antacid, H_2 antagonist, PPI at standard dose
- Advise follow-up if symptoms return or persist ≥ 1/week → other therapies

Take

Initial therapy for GORD
Standard dose PPI therapy
- All PPIs have same efficacy & adverse effect at equivalent doses
- Dosage: refer to "PPI standard dose", take 30-60 min before meal
- Day symptoms → take before breakfast
  Night symptoms → take before dinner
- Duration: 4-8 weeks
- Patients w/ atypical symptoms may need higher dose or longer duration

Review

Success →

Step-down therapies for GORD

↓Dose of PPI
- ↓ daily dose of PPI or dose on alternate days

OR

On demand PPI
- Take lowest effective dose of PPI when required (symptoms occur)

OR

Trial cessation of PPI
- Stop PPI, some patients will not relapse or symptoms can be managed by antacid or H_2-antagonist

If stepdown is not adequate to relieve symptoms, resume w/ lowest effective dose & frequency of PPI

Refer for endoscopy & specialist review
- Patient is refractory to PPI therapy or response is inadequate despite appropriate PPI & adherence
- Patient experiences red flags

Life-style measures
- Advise for lifestyle changes
- Lifestyle measures may help control symptom & ↓ meal-dependency

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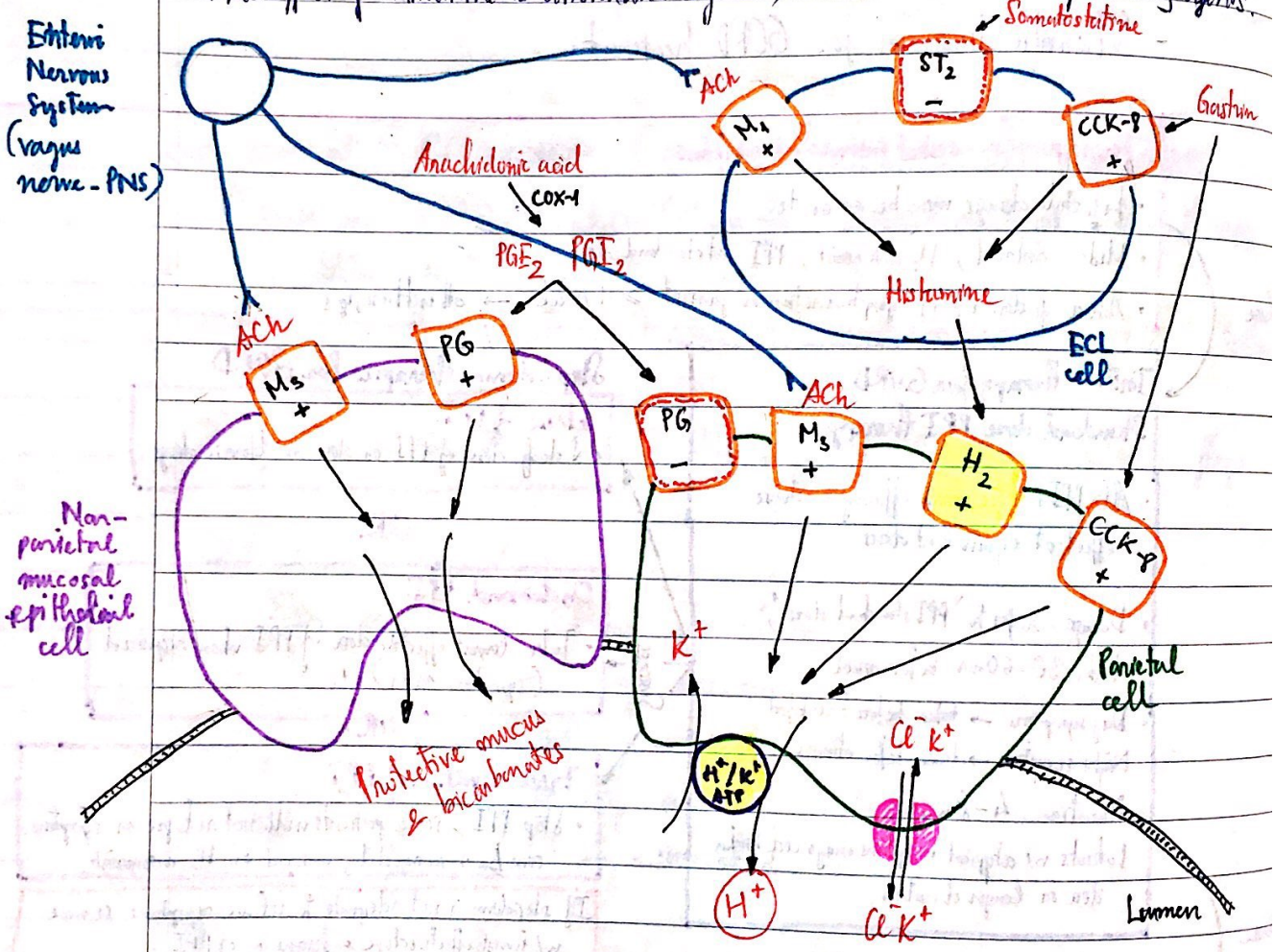
II) Therapeutics of antacids, H_2 antagonists & PPIs

Mechanisms that regulate acid secretion from parietal cells

- Acid secretion from the H^+/K^+-ATPase (proton pump PP) is triggered by hormones (eg. gastrin), neuronal factors (eg ACh) & paracrine factors (eg Histamine)
These chemicals either act through the enterochromaffin-like (ECL) cells or directly on parietal cells to stimulate acid secretion. The action on ECL cells releases histamine (act on H_2 receptors on parietal cells & activate cAMP dep pathway).
The effect of histamine is attenuated by PGs, which are mucosal protecting agents.



Patients suffering from GORD require the following:

- Relief of symptoms to improve quality of life
- Reduction in acid production to allow healing of esophagitis
- Reduction in risk of complication.

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Mechanism of antacids

- General, neutralizing stomach acid.
Although less effective than other drug classes, antacids are cheaper & widely available as OTC, have rapid onset.
- 3 classes of antacids:
  - Mg^{2+}/Al^{3+} compounds
  - Bicarbonates / Carbonates
  - Simethicone / Alginates

∞ Mg^{2+}/Al^{3+} compounds

- Examples:
  - $Al(OH)_3$; $Mg(OH)_2$
  - Combination of Al & Mg
  - $Mg_2Si_3O_8$: more usually used for peptic ulcer, slower onset, from colloidal silica.

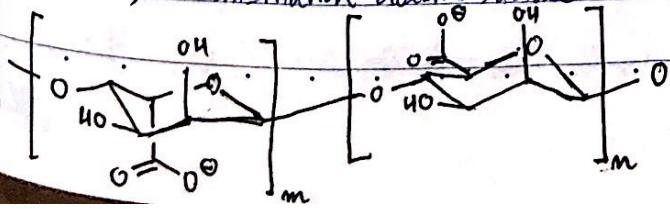
∞ Bicarbonates / Carbonates

- Examples:
  - $NaHCO_3$: readily absorbed, prolonged therapy can cause alkalosis & hypernatremia (heart & renal p.).
  - $CaCO_3$: same.

The reaction of HCO_3^-/CO_3^{2-} with HCl produce CO_2, which can stimulate gastrin secretion, resulting a secondary rise in acid secretion as well as belching, nausea, abdominal distention & flatulence.

∞ Simethicone / Alginates (not antacids strictly speaking)

- Simethicone is a surfactant : ↓ foaming, relieve bloating & flatulence
Alginates ↑ viscosity & adherence of the mucus to the mucosa → protective barrier
- Simethicone & alginates are usually included in antacids preparation to ↓ the incidence of GORD
However, the combination doesn't reduce antacid requirement.



Alginate.

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∞ Adverse effects & drug interactions

- Caution when taking gram amounts of Mg & Al salt. Some for HCO_3^-
- As both Mg & Al compounds are excreted by the kidneys, their long term use is not advisable w/ renal insufficiency:
  - Mg in chronic renal failure → Hypermagnesemia
  - Al in renal failure → Osteoporosis, encephalopathy, proximal myopathy
  - $NaHCO_3$ → Systemic alkalosis
  - Long term $CaCO_3$ → Hypercalcemia, Hyperphosphatemia

- Antacids ↑ gastric & urinary pH → alter ADME of other concurrent drugs
  Al & Mg are also chelating agents in the GI tract → ↓ absorption
  Most drug-drug interaction can be avoided if antacids are taken 2 hours before the main drug
- Some examples of ADME alteration w/ antacids:
  - ↓ bioavailability: Indomethacin, Theophyline, Phenytoin, Ketoconazole, Prednisone, Benzodiazepines, Ranitidine, Atenolol
  - ↓ elimination: Amphetamine, Ephedrine, Pseudoephedrine, Quinidine, Mecamylamine
  - ↓ hep. metabolism: Cimetidine
  - ↓ dissolution: Ketoconazole
  - ↓ efficacy: Nitrofurantoin (UTI)
  - ↑ bioavailability: Metoprolol
  - ↑ dissolution: Sulfonamide (acidic)
  - ↑ absorption: Levodopa, sulfonamide (acidic)
  - ↑ elimination: Salicylates, Phenobarbital

Mechanism of H_2 antagonists & their pharmacology

- 4 H_2 antagonists have been developed for clinical use, including GORD. All these drugs are well-absorbed, & differ mainly in their pharmacokinetics & potential for drug interaction
  - Ranitidine
  - Famotidine
  - Nizatidine
  - Cimetidine

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- H_2 antagonists are relative, competitive against histamine for binding to H_2 receptors.
Due to selectivity → little effect on other physio function
Basal acid secretion occurs via H_2-stimulated-cAMP-dependent pathway
→ H_2 antagonists are effective in ↓ basal acid secretion
↳ H_2 antagonists also suppress nocturnal acid secretion, but to a lesser extent on food-stimulated secretion

- Although less effective than PPI for controlling reflux, healing esophagitis or maintaining remission, H_2-antagonists may be useful for mild intermittent symptoms & when PPI is not suitable.

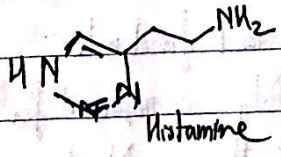
∞ Drug interaction & adverse effects

- pH neutralizer (eg antacid) can affect bioavailability of H_2 antagonist.
Eg: Antacids ↓ bioavailability of Ranitidine

- Cimetidine inhibits hep enzymes, eg CYP1A2, 2C9, 2D6
→ Alteration of drug pharmacokinetics.
Ranitidine has less interaction w/ CYP enzyme compared to Cimetidine

- Relapse of GORD can occur when H_2-antagonist treatment is stopped. However, H_2-antagonists are safe for long term use (well tolerated, low incidence)
Common side effects are minor:
- Disturbance in GI motility
- Headache, drowsiness, fatigue
- Muscular pain

∞ H_2 antagonist dev

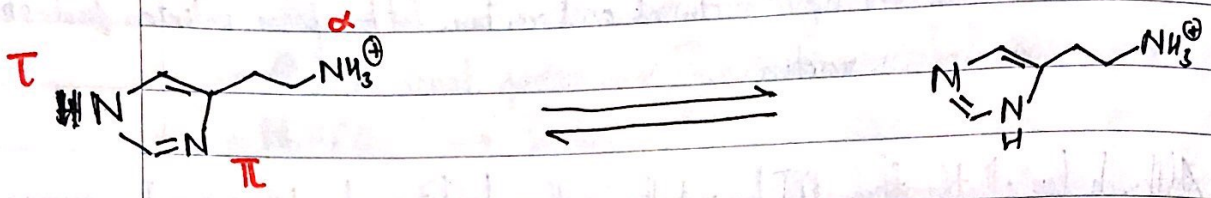


Histamine

- Endogenous ligand: Histamine
2 types of Histamine receptors:
- H_1: inflammation
- H_2: gastric acid production

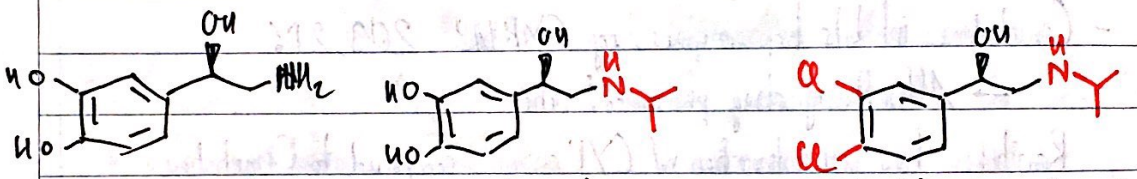
- Classic antihistamines have no effect on acid release since they are H_1 selective
  → Design the H_2 specific antagonist by understanding histamine structure.

- Histamine has 2 tautomeric forms : either the N_π or N_τ is protonated.

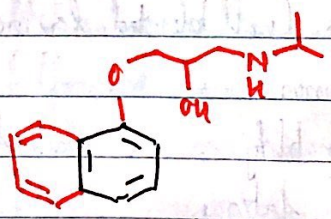


- In solution, NH_τ is favored (4 : 1 ratio)
- pK_a of $NH_3^+ \alpha$ = 9.8 → protonated at physio pH
- pK_a of imidazol = 5.4 → mostly neutralized.

- Dev of H_2 antagonist is in the same fashion as dev β antagonists agonist from Noradrenaline :



Noradrenalin | Isoproterenol β-agonist | Dichloro-isoproterenol β-antagonist



Propranolol
β antagonist

- Important functionals:
  - N_π is important for H_1 binding
  - Both ring N atoms of the imidazole ring needed for H_2 binding
  - 4-methyl histamine is H_2-selective
  - 4-methyl histamine favors the NH_τ tautomer

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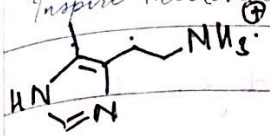
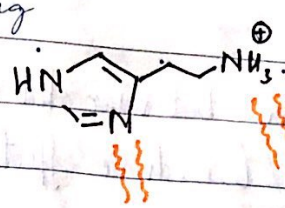
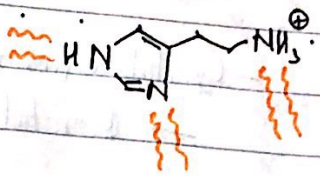


4-methyl histamine

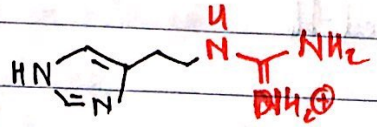


H_1-receptor



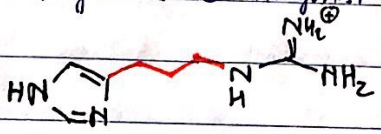
H_2-receptor

- Initial structure-activity relationship of histamine
  - Replacement of imidazole ring w/ other rings lost activity & antagonism
  - Guanidine analogue of histamine proved to be a partial agonist



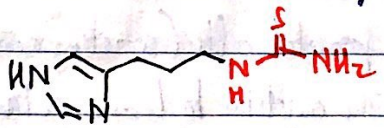
Guanidine analogue

- Lengthening the C chain gave some antagonist properties: (still a partial agonist)



3C chain (partial agonist)

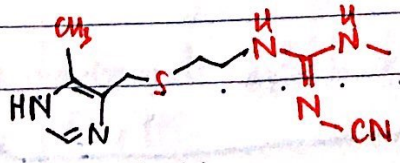
- Hypothesis: the antagonist binds to other site of the receptor other than where the aliphatic N would usually bind → change from basic guanidine to thiourea → weak antagonist



- Drawbacks:
  - pK_a of this imidazole ring is 7.25 → half ionized
  - N_π must be protonated
  - Thiourea was toxic

→ Changes:
- Thiourea → cyanoguanidine
- Additional 4-methyl group & an S atom in the chain → Stabilize imidazole ring & favor NH_τ tautomer

→ Cimetidine



Cimetidine

- Cimetidine was successful, but associated w/ many drug interactions
  → Ranitidine w/ less adverse effect.

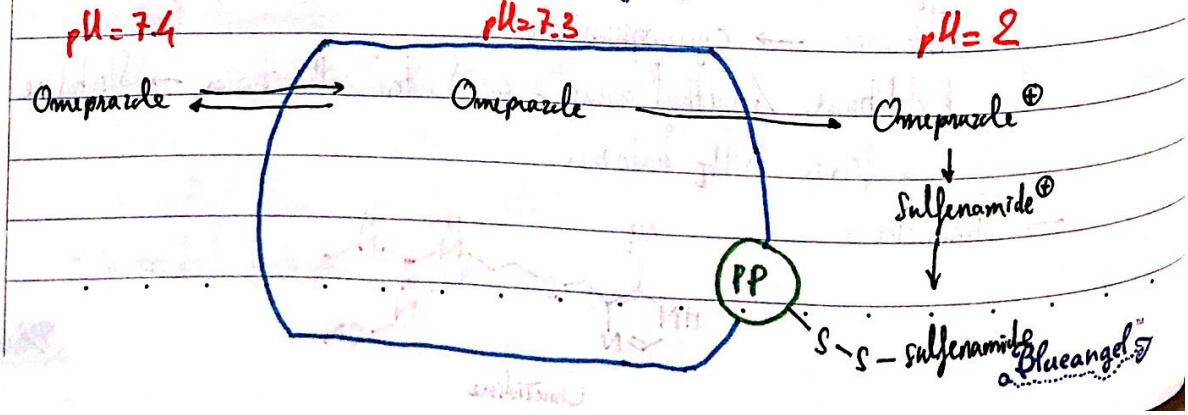
Mechanism of PPIs

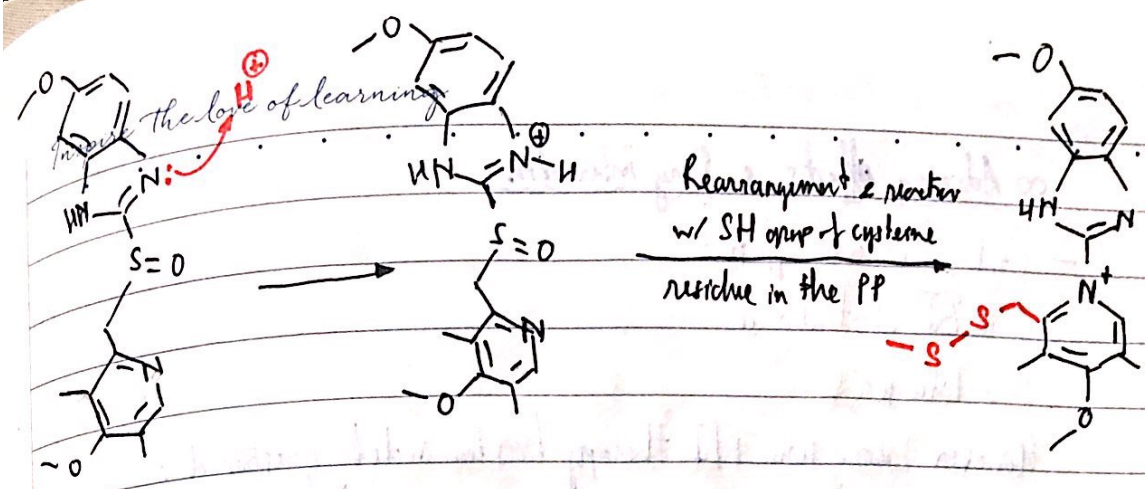
- PPIs are effective in ↓ basal acid secretion as well as food-stimulate secretion via the suppression of gastrin, Ach, histamine induced secretion
PPIs are primarily used for peptic ulcer, more effective than H_2 antagonist in controlling symptoms, healing esophagitis.
Examples of PPIs available:
  - Omeprazole
  - Esomeprazole
  - Lansoprazole
  - Pantoprazole
  - Rabeprazole
  - Dexlansoprazole (R-isomer of Lansoprazole)

∞ Properties of PPI

- PPI : irreversible inhibition & selective
They act on activated parietal cells (secreting acid). This is because PPIs are prodrugs which require acidic condition to become active
  → Inactive in blood (pH = 7)
  ↳ Active in lumen (pH = 2)

Eg : Omeprazole is converted into the active form of sulfenamide, which then forms covalent bond w/ the sulfhydryl group of cysteine residues in the proton pump





Formulation of PPIs & dosing

- PPIs are unstable in acid → Formulations to prevent degradation by luminal acid to bioavailability
  → Delayed-release or enteric-coated

- Some special formulation
  - Enteric coated pellets w/ gelatin capsule: Omeprazole, Dexlansoprazole, Esomeprazole, Lansoprazole, Rabeprazole
  - Delayed-release tabs: Omeprazole
  - Delayed-release caps: Dexlansoprazole, Esomeprazole
  - Delayed-release suspension: Esomeprazol, Omeprazole, Pantoprazole
  - Enteric coated microgranules in orally disintegrating tabs: Lansoprazole
  - Enteric coated tabs: Pantoprazole, Rabeprazole, Omeprazole
  - Caps & oral suspension: Powdered Omeprazole + $NaHCO_3$

- The number of PP ↑ after fasting & food-stimulated acid secretion
  → Best to take PPI 30mins before meal
  PPIs are rapidly absorbed, high plasma protein binding, extensively metabolized by CYP2C19 & CYP3A4. Genetic polymorphism of CYP2C19 in Asian are correlated w/ slow metabolism of PPIs

- Rebound acid hyper-secretion may occur after long term PPI, & rebound after ceasing may cause dyspepsia

- Dose of Esomeprazole & Lansoprazole should be ↓ in hep impairment due to the reduction in clearance of these PPIs

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∞ Adverse effects & Drug interactions

- Only few side effects :
  - GI disturbance
  - Nausea

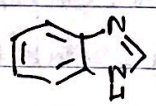
However, long-term PPI therapy has been widely questioned :
- ↑ risk of infections eg. hospital acquired pneumonia, spontaneous bacterial peritonitis
- Fracture risk
- B_{12} & Mg malabsorption

- Contraindicated w/ drugs that are metabolized by CYP2C19 & CYP3A4
Omeprazole (only) inhibits CYP2C19 & induces CYP1A2.

Loss of gastric acidity may affect bioavailability of other drugs eg. ketoconazole, ampicillin, Fe salt (similar to antacids' effects).

∞ Brief chemistry of PPIs

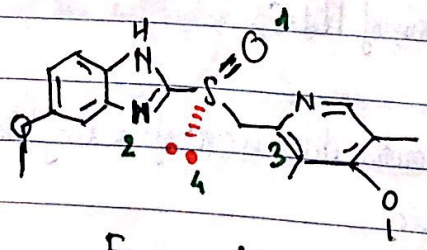
- PPI structures require a common scaffold consisting of both benzimidazole & pyridine



Benzimidazole

Pyridine

- The S atom in the structure is tetrahedral in geometry & has 4 different groups attached
  → Stereoisomer S & R
  Eg: Esomeprazole is an S isomer



Esomeprazole

* Lone pair is the lowest rank

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Week 5 of learning 26/3/2018

I) Pathophysiology, symptoms & diagnosis of IBS

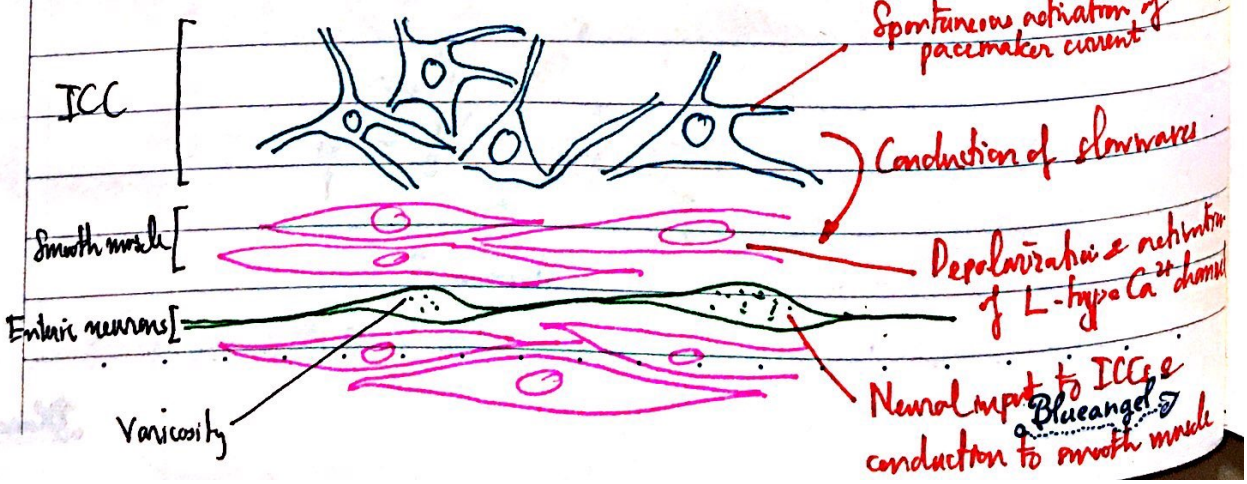
Mechanism of normal intestinal motility

- The GI tract has many roles:
  - Motility
  - Absorption
  - Secretion

Gut function are controlled by various complex mechanisms eg: network of enteric nervous system (ENS) & the autonomic nervous system (ANS)
Although ENS is considered apart of ANS, it can function without input from CNS

- Intestinal motility → muscularis externa relax & contract rhythmically, regulated by:
  - Nerves - myenteric plexus & extrinsic innervation
  - Interstitial cells of Cajal (ICCs)
  - Gut hormones - gastrin & motilin

ICCs are star-shaped cells in close proximity to the myenteric plexus, embedded within the smooth muscles
→ Pacemaker cells generate periodic waves of depolarization, however not causing contraction
→ Nerve stimuli & hormones are required to raise potential in the ICCs to exceed threshold to generate action potential
→ ICCs responsible for peristaltic reflex in small intestine & in lesser extent large intestine



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Contractility depends on the state of eating & fasting

- Fasting: the electrical activity in the gut is called migrating myoelectric complex, & the accompanying contraction is called migrating motor complex (MMC)
  the MMC is initiated by motilin, & sweeps thru gut to remove undigested objects & clears foreign materials
  → Cleaning the small intestine
  MMC prevent reflux of bacteria into the small intestine → prevent luminal bacterial overgrowth
- Fed: feeding disrupts MMC as food suppress motilin & promote gastrin release
  → Activation of digestive enzymes eg. pepsinogen

What happens during peristalsis

- Peristalsis → wave contraction of muth muscles to push the bolus toward the end.
- Chemicals & chemical stimuli induce the release of serotonin (5-HT) from the mucosal ECL cells.

Activation of other sensory neurons → release of other neurotransmitters called calcitonin gene-related peptide (CGRP) → activates inter neuron in the oral-caudal direction

- Oral side: Ach excites motor neurons, release neurotransmitters → circular contraction
- Caudal side: Somatostatin releases inhibitory chemical eg NO, VIP → circular relaxation
- On both sides: endogenous opioids called enkaphalins inhibit muscle contraction

Constipation & Diarrhea

Constipation

- Slow gut transit or ↓ ICCs → Less bowel motion
  - < 3 a week
  - Hard & dry stool → difficult & painful to pass
- Some reversible causes:
  - Lack dietary fibers
  - Meds eg. opioids, antimuscarinic
  - Hormonal changes
  - Neurological disorder
  - Systemic illness

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Intestinal secretion & Diarrhea

- Gut regulates whole body fluid & electrolyte homeostasis. Large vol of fluid pass thru the GI tract but later be absorbed by the large intestine (90%)
  → Secretion & Absorption to prevent imbalance
- One of the function of gut secretion is protection from bacteria & toxin
  Secretion occurs in the epithelial cells of the crypts, regulated by interplay between the endocrine system (hormone), ENS (submucosal neurons) & immune system (Immune

- Cl^- ion are secreted predominantly thru the cystic fibrosis transmembrane conductance regula (CFTR) chloride channels, & this secretion will be accompanied by Na^+ & H_2O, occuring via paracellular route

Trigger factors (secretagogues)
- Neurotrans eg. ACh, VIP from ENS nerve endings
- 5-HT from ECL cells
- Guanylin – a peptide synthesized by enteroendocrine cell & released into the lumen
- Bacterial enterotoxin
- Histamine
- Prostaglandins from myofibroblasts

- Diarrhea occurs when excessive stimulation of Cl^- secretion
  → Exceeding absorbing capacity of the large intestine

Based on causes → 2 types of diarrhea:
- Secretory diarrhea:
  + Secretion stimulated by infective agents
  + 90% of acute diarrhea
  + High risk groups: Travellers, Bed fevol, Immunodef., Daycare attendees, Ho
  + Bacteria may cause Cl^- secretion: Cholera, E. coli, C. diff toxin, Samon
- Osmotic diarrhea
  + Caused by defects in digestion and/or absorption → Nutrients stay in the lum
    → Draw water out → Loose stool
  + Lactose intolerant individuals are high risk

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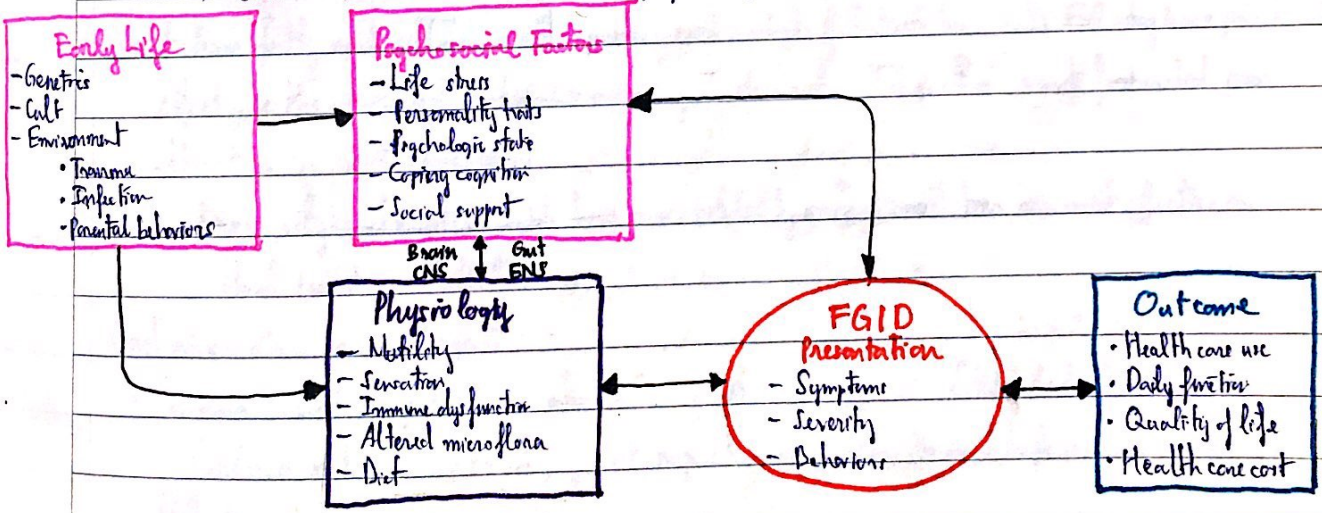
The definition & types of IBS

- Irritable bowel syndrome is a functional GI disorder, characterized by recurrent abdominal pain w/ either an alteration in stool form or frequency or defecation-related.
IBS is considered to exist on a long spectrum, where patient may change subtypes overtime due to the linked pathophysiology
Subtypes of IBS include constipation, diarrhea, mix & unclassified
→ Stool consistency based on stool chart:

- Criteria of IBS:
Recurrent abdominal pain, on average, at least 1day/week in the last 3month, plus ≥2 of:
  - Related to defecation
  - Change in frequency of stool
  - Change in form of stool

Pathophysiology of IBS

- Most are not well understood
- "Biopsychosocial model" influenced clinicians to look beyond biological cause
→ Genetic, environment, social, psychological factors together.



- Examples of influences of the "Biopsychosocial model" on IBS:
  - Social culture can shape the reporting of symptoms (eg diarrhea is considered normal in Mexico)
  - Salmonella infection as a child can be a risk factor for IBS as an adult
  - Patient attitude & family behavior → health care seeking

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Type 1: Separate hard lumps

Type 2: Sausage shape but lumpy

Type 3: Like sausage but w/ cracks

Type 4: Smooth & soft sausage

Type 5: Soft blobs w/ clean cut edges

Type 6: Mushy stool

Type 7: Entire liquid

- Psychiatric distress & maladaptive coping strategy can worsen GI symptoms
- Stress & maladaptive cognition can self-perpetuate symptoms
- Disturbed GI motility → Abnormal small bowel & colonic transit
  → Nausea, vomit, diarrhea & acute abd. pain
- Combination of abnormal stimulus: ↑gas production, visceral hypersensitivity, abnormal central pain processing
  (Lower pain threshold to colonic distention was observed in most IBS patients)
- Microbiome differences: the bacteria flora in IBS may be less diverse
  → Probiotics may help but need more research.

* IBS-C : constipation predominant IBS
IBS-D : diarrhea predominant IBS

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II) Management of IBS

Non-pharmacological treatments for IBS

- First step in treatment of IBS-C → Dietary advice
- Common triggers include : caffeine, alcohol, Carbonated drinks, ↓ fiber, lactose containing food, wheat

~ Fiber

- Mass, softness & hydration of the stool depend on fiber. Fiber resists enzymatic degradation
  → Stay unchanged in the large intestine

In the large intestine, whether or not the fiber is fermented by colonic bacteria depends on the composition of the dietary fiber, which also contributes subsequently to the transit of stool & its appearance

Type of Fiber	Example	Source	H_2O solubility	% fermentation	Effects on stool
Non-polysaccharide	Lignin	Wheat bran	Poor	0	↗ weight
	Cellulose	Cellwall of plants	Poor	15	↗ bowel mobility
Non-cellulose polysaccharide	Hemicelluloses	Fruits & veggies	Good	56-87	Highly fermentable, less effect on stool transit
	Mucilage	Higher conc. in edible plants	Good	85-95	↗ colonic bacterial mass
	Pectin		Good	90-95	Highly fermentable, less effect on stool transit

- Short chain fatty acids (SCFA) are the primary end products of fermentation. SCFA may have pro-kinetic effect, & the increased bacterial mass may ↑ stool vol. Fiber that is not fermented can attract water & ↑ stool mass
  → Non-polysaccharides which have poor solubility & % fermentation are most effective in stool transit & ↑ stool mass
- Contraindication & Side effects
  - Contraindicated in patients w/ obstructive symptoms, megacolon (dilated colon) or megarectum (dilated rectum). Instead, fecal impaction should be treated before fiber supplement.
  - Bloating but decrease w/ time

~ Lifestyle

- Exercise is recommended
- ↑ fluid intake
- Immediate response to urge (gastrocolic reflex is maximal at this point)

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~ Fermented carb. & Gluten

- Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAPs) are a
  to generate IBS symptoms due to their fermentation & Osmotic effects
  Fermentation ↑ colonic bacterial mass & is able to hold water in the intestine → ↓ stool
- High FODMAP diet can lead to abdominal pain, bloating, flatulence & diarrhoea
  → Low FODMAP diet and/or gluten-free diet may be beneficial in all IBS subty
  but predominantly in preventing IBS-D
- Sources of FODMAPs:
  - Some fruit (eg apple, peach)
  - Artificial sweeteners
  - Lactose containing food
  - Legumes
  - Some green veg (eg broccoli, cabbage)
- Sources of Gluten
  - Wheat
  - Rye
  - Barley
  - Malt
  - Brewer's yeast

Pharmacological treatments for IBS

~ Constipation & IBS-C

- Pharmaco treatment commence if
  - Diet & lifestyle changes is not enough
  - Fecal impaction
  - Patient starting opioid treatment
- Constipation in IBS-C can be managed the same way as functional constipation but IBS-C
  patient may not tolerate some types of osmotic laxatives or fiber (due to side effects)
  Stimulant laxatives may cause cramping in IBS-C
- Laxatives are classified based on their mechanisms of action:
  - ↑ luminal fluid retention
  - ↓ net absorption of luminal fluid
  - Altering GI motility by ┬ inhibiting segmental contraction
    └ promoting propulsive movements

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Drug class	Examples	Mechanism of action	Indication
Bulk forming	Psyllium, Ispaghula husk, Sterculia	• Absorb water in the colon to ↑ fecal bulk → Stimulate peristaltic activity	Constipation
Osmotic laxatives	Sorbitol, Lactulose, Macrogol/Polyethylene glycol, Saline laxatives	• Create osmotic load, draw water into lumen & lubricate	• Constipation • Fecal impaction • Bowel preparation before surgery
Stimulant laxatives	Bisacodyl, Senna, Sodium picosulfate	• Direct stimulation of nerve endings → ↑ motility • May cause accumulation of water & electrolytes in colonic lumen	• Constipation • Bowel preparation
Stool softeners or surfactants	Docusate, Liquid Paraffin, Poloxamer	• Assisting mixture of water into feces → Softening • May ↑ intestinal fluid secretion → Lubricate to facilitate passing	• Constipation • Prevent straining following rectal surgery & acute perianal disease
Opioid antagonists	Methylnaltrexone	• Peripherally acting competitive antagonist → Block opioid effect (not centrally)	• Opioid-induced constipation in palliative care & when other laxatives are inadequate
Prokinetic agents	Prucalopride	• $5HT_4$ agonist → ↑GI motility	• Chronic idiopathic constipation when other regular laxatives are inadequate

~ Diarrhea & IBS-D

- Rationale for drug use:
  - Prevent dehydration & electrolyte disturbance
  - Relieve symptoms
  - Treatment of infection

Before treatment, assessment on dehydration & electrolyte balance is prioritized in all cases, & diarrhea secondary to fecal impaction should be excluded.

- Acute diarrhea is usually due to pathogenic microorganism & standard treatment is oral dehydration salt (ORS), Others are opioids

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Drug class	Examples	Mechanism of action	Indication
ORS	Glucose & Salts containing Solution	Co-transportation of glucose & sodium by enterocyte → H_2O absorption	Correction of fluid & electrolyte loss in diarrhea
Opioids	Codeine, Diphenoxylate Loperamide	Action opioid receptor on gut wall → ↓ GI motility & ↑ fluid absorption	• Short term diarrhea treatment in adult • Intestinal stoma Cx ↓ frequency & fluidity of motions
Bile acid binding resin	Cholestyramine	Bile acid malabsorption	• IBS - D (off-label) • Diarrhea following ileal resection • Rarely used
Non-fermentable insoluble fibre	Sterculia	Bulking agent	• IBS - D • Rarely used.

- Use of opioids:
  - Except codeine, opioids act peripherally → more preffered.
  - Excessive use → constipation & toxic megacolon
  - Diphenoxylate can have CNS effect at high dose (addiction) & antimuscarinic effect (nausea, dry mouth, blurred vision)
  - Loperamide at high dose can cause constipation, CNS depression & paralytic ileus
  - Loperamide should be avoided in active inflammatory bowel disease of the colon to prevent toxic megacolon
  - Loperamide lacks abusive potential & is more effective than Diphenoxylate in treating diarrhea

- Anti-spasmodic may help control abdominal pain & occasionally diarrhea in IBS
  They are antimuscarinic, competing w/ ACh at postganglionic parasympathetic nerve endings → Inhibit smooth muscle contraction → ↓ GI motility & spasm
  Eg: Hyoscine butylbromide, Mebeverine, Peppermint oil (have anti-spasmodic & blocking Ca^{2+} channels) normalizing transit time & calminative effects)

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Management of IBS abdominal pain

- Antispasmodics
- Herbal prep STW5 (Iberogast). Analgesics are generally ineffective in abdominal pain
- Do not use opioids due to dependence & risk of narcotic bowel syndrome

~ Antidepressant therapy in IBS

- Stress can worsen IBS symptoms → the use of antidepressants, even for those without depression
  - SSRIs eg. Sertraline, TCAs eg. Amitriptyline are most effective
  - Used at lower doses than when used in depression:
    + TCAs are best for IBS-D due to anti-muscarinic effects of TCA
      → Side effects: constipation, dry mouth, drowsiness
      → Use may be limited to those w/ symptoms dominated by abdominal pain
    + SSRI are preferred in patients w/ depression/anxiety dominant feature.

~ Modifying gut microbiota

Gut microbiota can play a role in the cause of IBS
→ Modify gut microbiota.

- Rifaximin:
  - Non-absorbable member of antibiotic rifamycin
  - Used for IBS-D (non IBS)
  - Mechanism unclear. May due to reduction of GI bacterial load & change bacterial composition or activity

- Probiotics:
  - Reduce some IBS symptoms: bloating, flatulence & pain score
  - Lack of evidence

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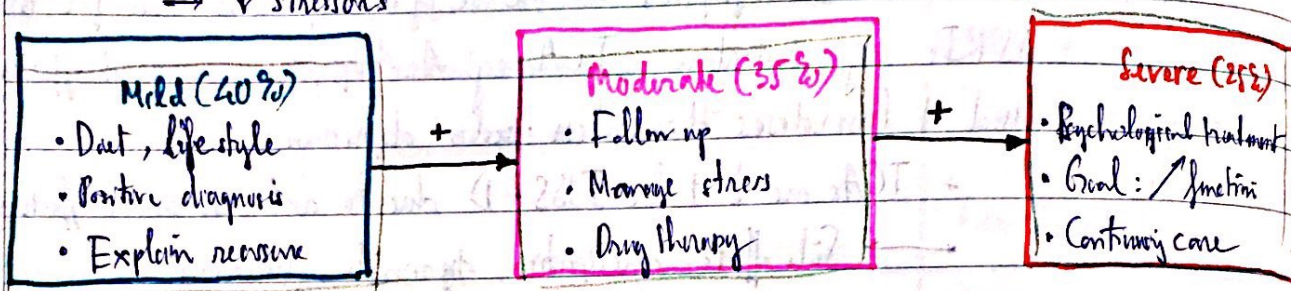
∾ Psychological therapies

- Cognitive - behavioral therapy
- Dynamic psychotherapy
- Hypnotherapy

- These psychological therapies have a large role in patients w/ severe symptoms & may have failed other treatment
  → ↓ stressors



Referral symptoms

- Red flags:
  - Family history of bowel cancer or coeliac disease
  - > 50 yo at onset of symptoms
  - Significant weight loss
  - Large-vol diarrhea
  - Steatorrhea (fat in feces)
  - Persistent vomiting
  - Severe abdominal pain
  - Fever
  - Sleep disturbed by symptoms
  - Evidence of GI bleeding (rectal, hematemesis)

Week 6 : 9/4/2018

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I) Smoking cessation

Quitline

- Quitline : giving up smoking service
  - Provide counsellors w/ experience & Quit specialist
  - Confidential
  - Enquiries about smoking history, motivation to quit → understanding habit, addiction
    → Tips on dealing w/ cravings, withdrawing, weight & stress
  - Follow-up
  - Customizable : interpreter, managing plan

- Cigarette smoke contains > 4000 chemicals in the form of gases or particles, & > 60 have been identified as cancer-causing chemicals, including:
  - Benzene
  - 2-naphthylamine
  - 4-aminobiphenyl
  - Chromium
  - Cadmium
  - Vinyl chloride

Nicotine in tobacco doesn't cause cancer, but it can stimulate the nervous system → ↑ heart rate & blood pressure, tightens small blood vessels under skin & causes wrinkles.

Nicotine dependence

- Nicotine = stimulant psychoactive drug

2 important contributors to why people are unable to stop smoking, even w/ their health & wellbeing are impacted:

- Physical dependence : exposure to nicotine results in reversible, pharmacological changes in tissue, neurotransmitters/modulator or receptor responses that alter basal physiological function → withdrawal symptoms & consumption of the drug to avoid disturbances

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- **Psychological dependence**: long-lasting changes in the brain plasticity, drive alterations in behavioral outcomes & decision making processes. (while reversible these changes are difficult to overcome). Changes in strength of neuronal connections, & within brain systems that control behavior & motivation → urge to take drug → craving, may not resolve after cessation

∾ Mechanism underlying nicotine dependence

- Nicotine promotes reinforcement of drug-taking behaviors where users experience a desirable stimulus → positive reinforcement
- Nicotine promote reinforcement of drug-taking behaviors where users use the drug to remove an undesirable stimulus (eg. craving, anxiety) → negative reinforcement.
- Cues become associated w/ smoking (eg. smoking ashtray)
- Relapsing is common & can occur weeks & months after withdrawal symptoms have ceased.

- Nicotine ↑ dopamine release in the limbic system, particularly in the nucleus accumbens
  → Dopamine release is associated w/ naturally reinforcing events (food, sex)
  Dopamine release signals "unexpectedness" or novelty, & is important for movement & reward-related functions (goal-directed behaviors)

- Nicotine acts on nicotinic receptors, excitatory ion channel receptors
  → ↑ excitability of DA-ergic neurons & ↗ DA release → activate limbic system

∾ Acute & Chronic effects of smoking

- Cigarette smoke causes harm to nearly every organ, many diseases & ↓ health in general
  Exposure to smoke is linked w/ nasal irritation, nasal sinus cancer, lung cancer, COPD, asthma, chronic resp symptoms, impaired lung function

* DA: dopamine

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- Cancers:
  - Oropharynx
  - Larynx
  - Esophagus
  - Lung (resp. tract)
  - Acute myeloid leukemia
  - Stomach
  - Liver
  - Pancreas
  - Kidneys & ureter
  - Cervix
  - Bladder
  - Colorectal

- Chronic diseases:
  - Stroke
  - Blindness, cataract, age-related macular degeneration
  - Congenital defects - maternal smoking: orofacial clefts
  - Periodontitis
  - Aortic aneurysm, early abdominal aortic atherosclerosis
  - Coronary heart disease
  - Pneumonia, TB
  - Atherosclerotic peripheral vascular disease
  - COPD, asthma
  - Diabetes
  - Reproductive effects in ♀ (↓ fertility)
  - Hip fracture
  - Ectopic pregnancy
  - ♂ erectile dysfunction
  - Rheumatoid arthritis
  - Immune dysfunction

- For smokers, acute tolerance develops throughout the day due to desensitization of nicotinic receptors, & desensitization wears off overnight
  → Morning cigarette pleases smokers
  Chronic tolerance develops to adverse effects eg. nausea, palpitation, sweating,

clamminess → ↑ mg of intake per cigarette over time

- Since inhalation is a quick method to deliver nicotine to the brain
  → Huge risk of psychological dependence
  → Withdrawing symptoms lasting for months or years:
    - Craving
    - Irritability, anxiety, anger, impatience, restlessness
    - ↓ concentration
    - ↑ weight & appetite
    - Insomnia

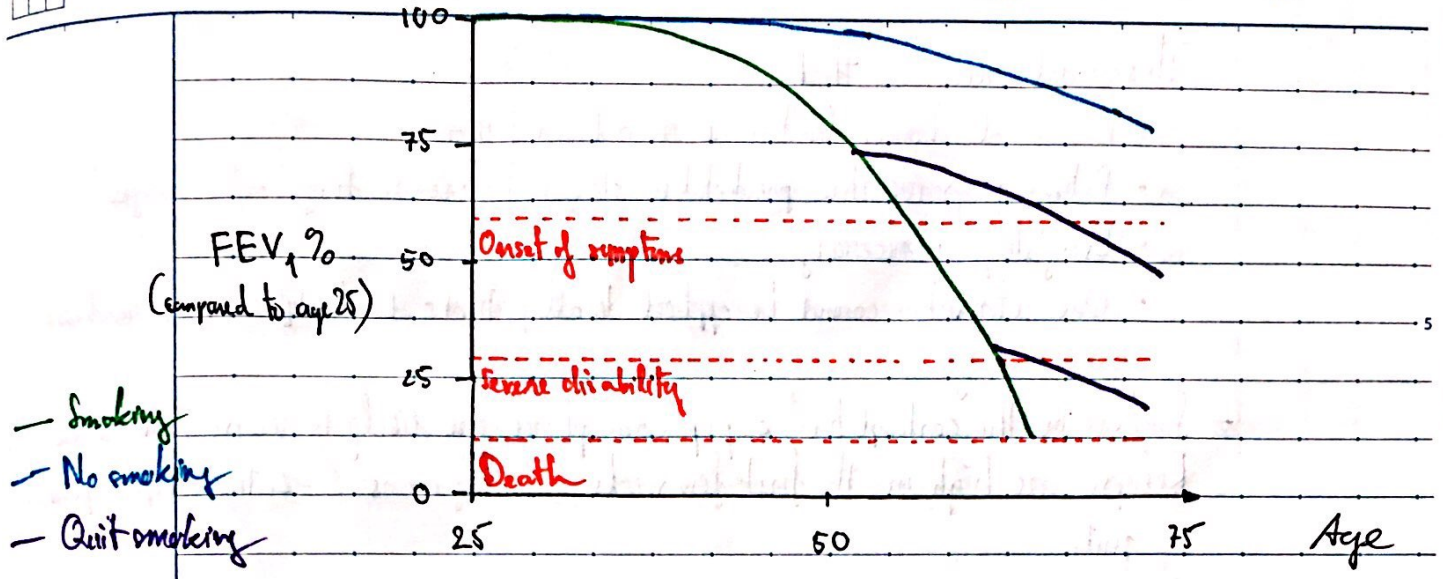
During abstinence following chronic smoking, there is a ↓ in baseline DA release & a ↓ ability to experience rewarding stimuli

Only few smokers can quit without abstinent symptoms, most exhibit craving & relapse behavior

Role of smoking cessation

~ Why?

- Health consequences of smoking are well-recognized, & the benefits are well-documented
  - ↑ taste & smell 5 days after quitting
  - ↑ skin appearance & physical fitness
  - 1/2 risk of cardiovascular events after 1 year, & as non-smoker after 15 years
  - 1/2 risk of lung cancer after 10 years
  - Same risk of having low birth-weight baby as a non-smoker for pregnant women who quit smoking in the early months of pregnancy



∾ Initiatives to promote smoking cessation:

- WHO Framework Convention on Tobacco Control has urged for better communication about various threats posed by exposure to tobacco smoke
- Australian Gov Dep. of Health also leads programs to ↓ smoking prevalence & associated health, social & eco cost. Control measures include:
  - Staged excise ↑ on tobacco product
  - Education
  - National tobacco campaigns
  - Plain packaging of tobacco products
  - Graphic health warning labelling
  - Prohibit tobacco ads
  - Support quitting, including nicotine replacement therapy in the PBS

∾ Options to quit

- Motivation is the key. Smoking intervention only works for those w/ motivation
- Stages of change model:
  - Pre-contemplation
  - Contemplation
  - Preparation
  - Action
  - Maintenance

} Relapse

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This model recognizes that:
- Behavioral changes don't occurs in a linear fashion
- Patient progresses thru predictable stages before reaching "action stage"
- Every stage is necessary
- One intervention cannot be applied to all patients due to differenses in readiness

- Smokers in the "contemplation" & "preparation" phases are likely to receive advice & intervention
Relapse are high in the first few weeks, usually occurs: 3 - 4 times before permanent quit.

The 5A's approach: & ABCD

- Provide evidence-based framework for structuring smoking cessation intervention

1. Ask

- Ask for: • Smoking status
• Smoking history (n° of cigarettes, strength, quitting attempts)
Documentation in medical record for every patient

2. Assess

- Nicotine dependence should be assessed in all patients, along w/ presence of quitting barriers & motivation to quit
→ Fagerström Tolerance Questionaire w/ 2 strong predictors:
• Time to 1st cigarette of the day (TTFC)
• Cigarettes per day (CPD)

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Fagerstrom Test for Nicotine Dependence (FTND)

Question	Answer	Score
How soon after waking up do you smoke your 1st cigarette?	≤ 5 mins	3
	6 – 30 mins	2
	31 – 60 mins	1
Do you find it difficult to abstain from smoking in places where it is forbidden?	Yes	1
	No	0
Which cigarette would you hate to give up?	The 1st one in the morning	1
	Any other	0
How many cigarettes a day do you smoke	≤ 10	0
	11 – 20	1
	21 – 30	2
	≥ 31	3
Do you smoke more frequently in the morning than in the rest of the day	Yes	1
	No	0
Do you smoke although you are sick in bed for most of the day	Yes	1
	No	0

Total score (level of dependence):
0-2 (very low); 3-4 (low); 5 (medium); 6-7 (high); >8 (very high)

Heaviness of Smoking Index (HSI) test

Question	Answer	Score
On the days that you smoke, how soon after you wake up do you have 1st cigarette?	≤ 5 mins	3
	6 – 30 mins	2
	31 – 60 mins	1
	> 60 mins	0
How many cigarettes do you typically smoke per day?	≤ 10	0
	11 – 20	1
	21 – 30	2
	≥ 31	3

Total score:
0-2 (low addiction); 3-4 (moderate); 5-6 (high)

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3. Advice

- Supportive & non-confrontational advices should be offered to all smoker at least annually
  Where possible, advice on the benefits of smoking cessation should be personalized
  Brief counseling is effective & every smoker should be offered at least this intervention at every visit.

4. Assist

- Help to set realistic personal goals for behavioral change
  Verbal & written advice could be provided
  Referrals could be made to smoking cessation support programs
  Offer assisting in choosing appropriate medication, based on nicotine dependence.

5. Arrange follow-up

- In-person or telephone should be organized, especially in the 1st week & month after quit day
  Review progress & issues
  Congrats for achievements & sympathize for relapse

~ ABCD

- Alternative to 5A's
  - Ask: all patient abt smoking
  - Brief intervention: provide interventions, including advices, written info, NRT, referral to relevant support
  - Communication & Discharge: about smoking status & action taken in discharge documentation

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Treatment options

- 1st line : NRT, bupropion, Varenicline
- Eligibility for PBS-subsidised smoking cessation therapy:
  - Patient must undergo concurrent counselling for smoking cessation via a comprehensive support & counselling program at the time PBS-subsidised treatment is initiated.
  - Must be for this condition
  - Restriction on number / duration of PBS-subsidised smoking cessation pharmacotherapy per 12 months:
    Eg: ≤ 12 weeks of NRT patches
    ≤ 24 weeks of varenicline
    ≤ 9 weeks of bupropion

Nicotine Replacement Therapy (NRT)

- NRT = tobacco without harmful constituents. It ↓ psychological dependence, delays weight gain & ↓ withdrawal symptoms.
- Different forms are available:
  - Patches
  - Gum
  - Lozenges & Mini-lozenges
  - Inhaler
  - Mouth spray
  - Sublingual tabs
- No form of NRT is significantly better than the others in terms of withdrawal symptoms, urge to smoke & rates of abstinence. However, patient compliance is different for each form.
  → Selection based on practical consideration & patient preference.
  High dose NRT requires monitoring for adverse effect.
- NRT combination (long acting + short acting) is recommended for patients w/ high nicotine dependence & those who continue to exp withdrawal symptoms w/ monotherapy.
- NRT is safe for pregnancy & breastfeeding, adolescence 12-17yo, pre-existing cardiovascular disease. However, monitoring is still required & should only be used when non-pharm therapies are not effective
- NRT lower concentration peak of nicotine than active smoking
  → Theoretically safer, even in patient w/ unstable disease

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∾ Prescription meds

- Both Varenicline & Bupropion are S4 items & only one treatment/year is subsidised thru the PBS. These are alternatives for smoker who cannot tolerate NRT
- Varenicline is known to be more effective than bupropion, & is the most effective, equally to NRT combination

∾ E-cigarettes

- Although not approved in Australia, some countries recommend e-cigs:
  - E-cigs contain liquid that is volatile, bringing nicotine, flavours & solvents eg: propylene glycol, glycerol or ethylene glycol
  - Can cause mouth, throat & eye irritation
  - Long term safety is unknown

∾ Smoking & other medicines

- Smoking can alter ADME of medicines:
  - Inducing liver enzymes CYP1A2
  - Enzyme activity return to normal → cautious w/ drugs w/ narrow therapeutic index (eg. clozapine, olanzapine, theophyline, warfarin)

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II) Co-existing respiratory & GI conditions

Asthma - COPD overlap syndrome (ACOS)

- Featuring both asthma & COPD symptoms
  Develop in smokers, ex-smoker, second-hand smoker, & is worse in old people
- Patients w/ ACOS are at higher risk than ppl w/ either condition alone, w/ more symptoms, flare-ups, needs for health care use & ↑ higher mortality

- ACOS should be considered in adult if they have:
  - History of asthma or asthma-like symptoms
  - Spirometry test shows no reversible after bronchodilator.

ACOS has: airway with ↑ eosinophiles, neutrophils, mixed pattern of airway inflammation, & may have systemic inflammation
→ Ranges of airway disease phenotypes w/ different causal mechanism

~ Assessments for ACOS diagnosis

- Spirometry for airway irreversible
  Eosinophilia test for asthma with ↑ treatment choice.
- Patients with ↑ eosinophil count (>3%) have been shown to respond better to ICS than patients without eosinophilia
  Blood eosinophil can provide estimation about airway eosinophilia

- Patients w/ ACOS have less emphysema & greater airway thickness compare w/ sole COPD
  Recap for differences in Asthma & COPD inflammation:
  - CD4 T_h cell, eosinophil → Asthma
  - CD8 T_h cells, neutrophil → COPD

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∞ Management & treatments

- Preventative measures, including lifestyle changes
Symptom management using bronchodilators

- For patients w/ COPD & asthma features of asthma, long-term ICS (at lowest effective dose) prevents serious flare-ups, even if asthma symptoms appear to be mild & infrequent.
Increasing dose of ICS when eosinophil count >3% to ↓ exacerbations

- Patients w/ ACOS experience more frequent exacerbations, ↓ quality of life, rapid decline in lung function, higher morbidity & mortality than those with either of two conditions.
An in-depth evaluation including a complete medical history, physical examination, pulmonary function tests & imaging is required to diagnose & classify properly

Eosinophilia in COPD can be a marker of response to ICS, or a predictor of exacerbation when steroids are withdrawn

- The use of the term "ACOS" is unclear for facilitating treatment decisions due to patients' different characteristic, especially in the absence of clinical trials addressing this heterogenic population

Asthma & GORD

∞ Relationship between asthma & GORD

- Although GORD is thought to worsen asthma control, the precise effect is unclear
2 possible mechanisms:
  - Damage to the pulmonary tree after direct exposure to acid reflux
  - Bronchial constriction as a result of the stimulation of vagal nerve endings in the esophagus

- In addition, cough & ↑ respiratory effort may worsen GORD by bringing about an ↑ pressure gradient across the LOS. This is of particular relevance in patients w/ hiatus hernia

as gastroesophageal junction competence is compromised by hiatus hernia during intra-abdominal pressure increases

- Many patients w/ asthma report symptoms of GORD or an abnormal result on the 24h pH test. Among children treated in referral clinics, the prevalence of GORD is higher among those w/ asthma than those without.

Asthma may also contribute to GORD via the effects of asthma meds on the gastroesophageal sphincter

Eg: Prednisone & Salbutamol may ↓ contracting ability of the LOS

Other bronchodilators may relax the smooth muscle of the esophagus → GORD

~ Diagnosis of GORD-related asthma

- Not always easy but this may help:
  - Monitoring & recording asthma symptoms in detail over a period of time
  - A 24h study of the esophagus to determine the presence & amount of reflux
  - A trial of PPI for 1-2 months to see the effects on asthma symptoms

~ Improve asthma control in patients w/ GORD

- In adults w/ asthma, manage GORD according to current guidelines for reflux, but doesn't advise patient that drug for reflux will improve asthma control

In adult w/ asthma & diagnosis of GORD, PPI treatments produce a small ↑ in lung function & quality of life

The effect of PPIs alone on asthma symptoms in patient w/ GORD is unclear, but the combination of a PPI & Domperidone (dopamine antagonist) may ↑ lung function & improve asthma symptoms

In patients w/ history of asthma symptoms related to reflux, H_2 antagonists may ↓ nighttime symptoms & reliever requirement.

PPIs should not be used for uncontrolled asthma symptoms in children or adults without diagnosis of GORD.

- There is limited evidence for the benefit of PPIs in children w/ asthma & GORD. Such studies are lacking in young children.

Subclinical or undiagnosed GORD is sometimes thought to contribute to asthma symptoms or poorly controlled asthma, leading to the hypothesis that reflux treatment may be useful in asthma management.

However, clinical trials do not support this strategy, but indeed, reflux can cause ↑ adverse effects (mainly resp infections) in children.

Asthma in special populations

∞ Aboriginal & Torres Strait Islander People (ATSI) & people from culturally & linguistically diverse (CALD) background

- Asthma hospitalization & rates of death are higher for ATSI

Detection, diagnosis & management of asthma may be complicated by ↑ rate of resp infections & chronic lung disease in remote ATSI communities

Cultural respect (including recognition, protection & continued advancement of the inherent rights, cultures & tradition) → key for sustainable healthcare system

- A range of psychosocial factors can affect asthma symptoms & outcomes in children & adults (biological, individual, family & community-level factors)

These can have synergistic effects of life circumstances on patients' & families' ability to manage asthma

Poor health literacy → poor asthma control due to poor knowledge of meds & techniques

- When working w/ CALD group, the followings should be considered:
  - Work w/ an interpreter
  - Consider patient's health beliefs, culture & family circumstances that may affect asthma management
  - Using & providing asthma self-management resources in the patient's 1st language, or that has been designed especially for that community.

- For every asthmatic, develop an individualized written asthma action plan (WAAP) that is appropriate for their regimen, asthma severity, culture, language, literacy level & ability to self-manage.

∾ Asthma in Pregnancy

- Asthma = most frequent chronic condition during pregnancy :
  - Poor asthma control ↑ risk of infant w/ low birth weight, preterm birth & pre-eclampsia (high blood pressure & protein in the urine during pregnancy)
  - Well control asthma ↓ risk of congenital malformations & birth/delivery complications
  - Children exposed to uncontrolled asthma during gestation have an ↑ risk of developing asthma. Fetal growth restriction can lead to ischemic heart disease, hypertension & type 2 diabetes in adulthood.
  - Properly treated acute asthma attacks don't adversely affect the pregnancy
  - Monitor & review asthma during pregnancy as changes in asthma control can change during gestation
    Eg: Changes in diaphragm position & chest wall in the third trimester may alter breathing efficiency.
  - Upto 50% women experience symptomatic GORD. Treating GORD in asthmatic women during pregnancy needs more research.
  - Allergic rhinitis can ↓ asthma control in pregnancy. Pregnant women may experience rhinitis-like symptoms of physiological congestion of nasal mucous membrane due to pregnancy hormones

∾ Safety of meds for asthma & comorbidities in pregnancy

- All inhaled meds under category A or B → no proven harm to fetus
  → Should not stop taking these meds without medical consultation.
- Many of the adverse events is due to poor asthma control, rather than the medication
- More safety data is needed on newer medication eg LABAs and LTRAs
- For allergic rhinitis, INCS is 1st choice treatment unless contraindicated.
- For GORD, PPIs are B3 & H_2 antagonists are B1

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- Manage asthma in breastfeeding women as for asthma in other adult, aiming to maintain the best possible asthma control & to control asthma flare-ups, while using the lowest effective doses. Use preventers as indicated, step up & down where appropriate
- Advise avoiding exposure to smoke

	Cat A	Cat B1	Cat B2	Cat C
Relievers	• Salbutamol Sulfate • Terbutaline Sulfate	• Salbutamol Sulfate (Atacomin)		
ICS	• Budesonide		• Beclometasone Dipropionate • Ciclesonide • Fluticasone Furoate Propionate	
ICS/LABA combination			• Budesonide/Formoterol Fumarate dihydrate • Fluticasone / Formoterol • Fluticasone Furoate/Vilanterol Trifenatate • Fluticasone Propionate/ Salmeterol Xinafoate	
Other preventers		• Montelucast sodium • Sodium cromoglycate		
Systemic corticosteroids	• Methyl prednisolone • Prednisolone • Prednisone			• Hydrocortisone
Other bronchodilators	• Adrenaline • Aminophylline • Theophylline	• Ipratropium • Tiotropium		
Allergic rhinitis nasal spray	• Budesonide	• Ipratropium	• Azelastine • Beclometasone • Ciclesonide • Fluticasone • Levocabastine • Mometasone	

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∞ Asthma & Pregnancy Planning

- Consider replacing current preventer w/ a ICS/A preventer, to see if asthma control remains stable
- Once stable on ICS/LABA combination, advise to continue & explain that stopping LABA can often lead to loss of asthma control
- If the woman is anxious to stop LABA before pregnancy, discuss risks/benefits of ICS monotherapy trial. If control is not maintained on ICS alone, the patient should be put back on the previous regimen

Severity	Symptoms	FEV_1 % predicted	Drug class	Comments
Mild Intermittent	≤ 2 day/week; ≤ 2 nights/month	≥ 80%	SABA	• Use as rescue therapy in all type asthma • Salbutamol is most safe
Mild persistent	3-6 days/week; ≥ 3 nights/months	≥ 80%	Low dose ICS	• Budesonide most safe, but other ICS also show same safety & efficacy (no evidence)
Moderate persistent	Intermittent daily; ≥ 4 nights/week	61-79%	Med-dose ICS or ICS/LABA	• ↑ ICS dose or adding LABA to ICS are equally safe • LABA should not be used as monotherapy - Salmeterol, but no evidence shows other LABAs are less safe or efficacious
Severe persistent	Continuous daily & nightly	< 60%	High dose ICS/LABA Oral steroid if needed	• Chronic oral steroid should be administered at lowest effective dose & for shortest period needed, especially in the 1st trimester

∞ Management of acute asthma/exacerbations in pregnancy

- To avoid maternal & fetal hypoxia, patients should be counselled to start rescue therapy at home when they have worsening of symptoms, eg. coughing, chest tightness, dyspnea, wheezing, < 80% FEV_1 % personal best.

With a good response, the patient can continue normal activity

If notice ↓ in fetal activity or lack of good response → immediately seek medical care

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- Inhaled SABAs are the rescue therapy of choice for asthma during pregnancy. In general, patients should use upto 2 treatments of inhaled salbutamol (2-6 puffs) or nebulized salbutamol at 20min intervals for most mild to moderate symptoms. Higher doses can be used for severe symptom exacerbation.

For a woman w/ asthma, oral corticosteroid should be commenced if indicated as other acute

Week 7: 16/4/2018

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I) Intro to pain, opioid chemistry & pharmacology of analgesics

Intro

∾ Pain definition

- Pain = unpleasant sensory & emotional experience associated w/ actual or potential tissue damage, or described in terms of such damage.
  → Pain can exist w/ or without physiological stimuli (mostly with)

- Pain processing normally begins with nociception
  ends with motor output or a conscious exp.

Pain serves as a warning signal to avoid harmful situation

∾ Pain classification

- Pain can be classified clinically :
  - Nociceptive : activation of normal pain fibers in response to a noxious stimulus, may be somatic (superficial structures) or visceral (deeper organs)
  - Neuropathic : injury/disease affecting the peripheral and central nervous system
  - Mixed nociceptive/neuropathic :

Types of pain → different responses to drugs & treatments

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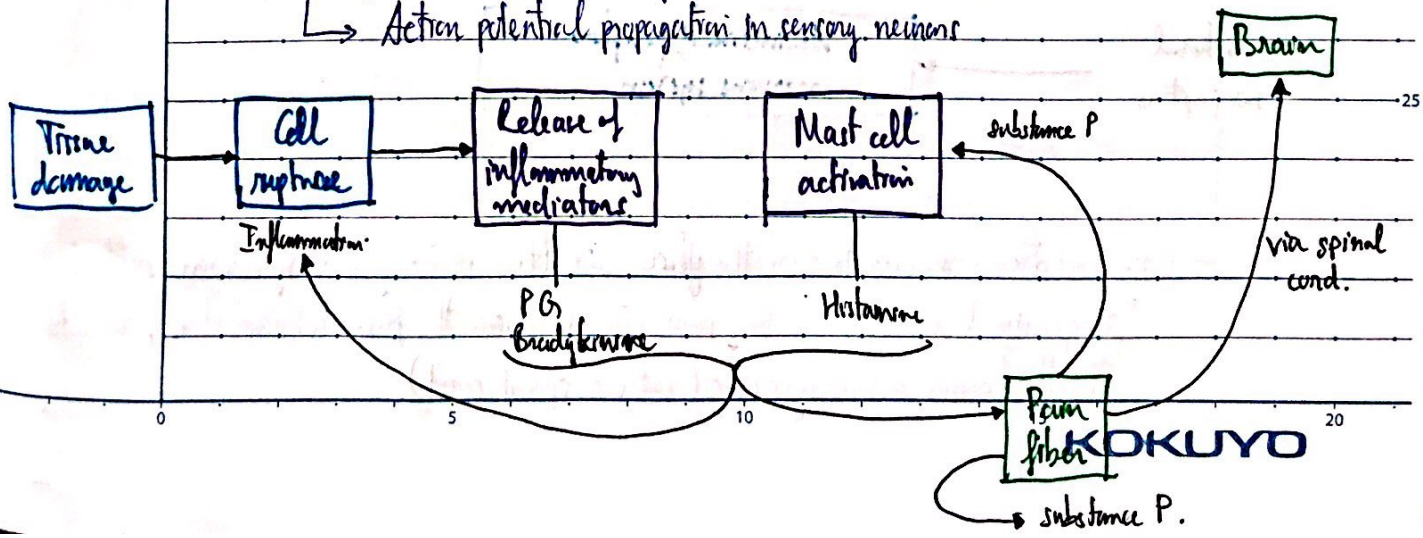
	Nociceptive - superficial somatic	Nociceptive - deep somatic	Nociceptive - deep visceral	Neuropathic
Origin of stimulus	• Skin • Subcutaneous tissues • Mucosa of mouth, nose, sinuses, urethra, anus	• Bones, joints, tendons • Superficial lymphnodes • Organ capsules & mesothelial membrane	• Solid or hollow organs • Deep tumor masses • Deep lymph node	• Damage to nociceptive pathway
Examples	• Burn • Wound • Ulcers • Stomatitis	• Muscular injury • Osteoarthritis • Bone fracture • Bone metastases	• Appendicitis • Myocardio infraction • Endometriosis • Diverticulitis	• Herpes zoster • Postherpetic neuralgia • Diabetic neuropathy • Poststroke pain • Phantom pain • Spinal cord injury
Description	• Hot • Sharp • Stinging	• Dull • Aching • Throbbing	• Dull • Deep • Gnawing, cramping • Pressure, tightness	• Dysesthesia (pain) • Allodynia • Hyperalgesia • Pain in a missing body part • Pain in a numb area
Localization	• Localized	• Poorly defined	• Poorly defined	• May be perceived in the territory supply by the affected nerves or pathways

Pain transmission to the brain

- Activation of nociceptors → exp. of pain, can be thermoceptor, chemoceptor or mechanoceptor.
  - ↳ Action potential propagation in sensory neurons

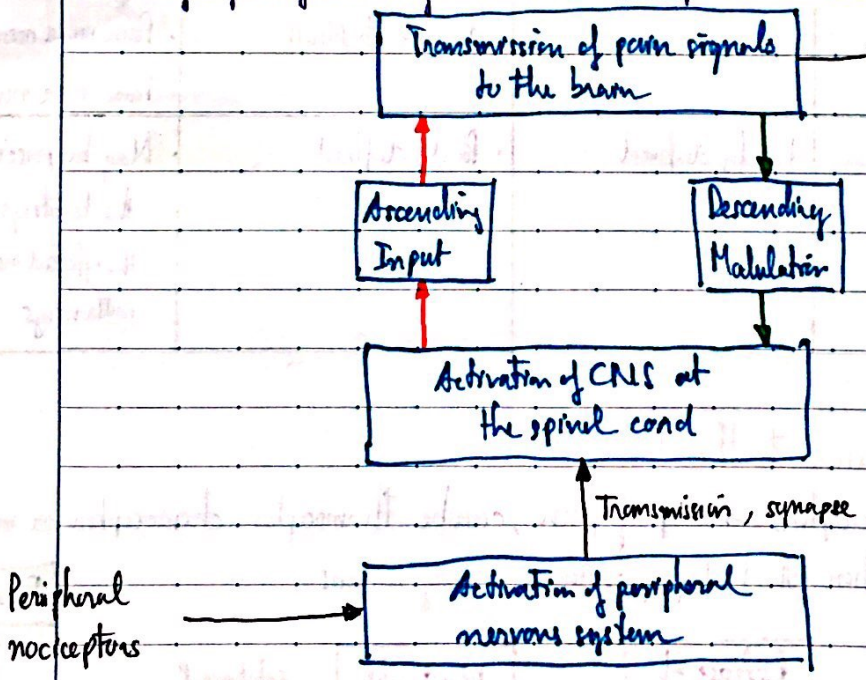


- Nociceptors can be found anywhere in the body.
  Eg. Poorly aligned vertebrae in the back can cause mechanoceptor stimulation
  → Back pain

Once nociceptors are activated, action potentials (pain signals) along the primary sensory neurons synapse in the spinal cord with secondary sensory neurons in the dorsal horn of the spinal cord, then to the thalamus & to the sensory cortex.

- Tissue injury, whatever the cause, causes many mediators to be released which can produce inflammation, & pain is only 1 in 5 main signs of inflammation (pain, redness, swelling, heat, loss of function). Heat may exacerbate pain since it activates thermoreceptors eg. TRPV1

Acute tissue injury can cause pain thru the release of chemical mediators eg PGs & Histamine, but the damaged area can stay inflammed & sensitive afterwards.
If a part of the body is more sensitive to pain → allodynia



- One exception: nociceptors on the face result in primary sensory neurons called "trigeminal neurons" sending pain signals from the face to brain stem, then to the thalamus & sensory cortex (not via spinal cord)

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The face is innervated w/ lots of sensory neurons, & large areas of sensory cortex is dedicated to the face.
→ Face is so sensitive

Modulation of pain reception

- Occur either in the brain, spinal cord or the periphery
Pain perception is different for everyone, remember gate theory.

- Descending pathways (pain modulation) are targets to treat both acute & chronic pain.

- Other parts of the brain may involve with the modulation of pain:
  - Lymbic system: if you have exp. unpleasant pain previously, pain sensation can be heightened
  - Frontal cortex: involved in the conscious & awareness of pain. → alter pain perception

Referred pain

- Many primary neurons can synapse onto a single secondary neuron that transmits pain signal to the brain. Because of this convergence of primary neurons, a disorder of an internal organ is sometimes perceived as cutaneous (skin) pain.

Eg: Cardiac ischemia, where neurons from the heart converge w/ those from arm & shoulder → Pain can be felt in the neck, shoulder & left arm.

- Other examples:
  - Pain from esophagus: upper abdomen, throat
  - Pain from heart: throat, shoulders, left arm, neck, back head
  - Pain from urinary/bladder: perineal area, penis.
  - Pain from left ureter: left down abdomen & back
  - Pain from right prostate: right down abdomen, thigh & leg.

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- There are numerous acute pain types, but will focus on:
  - Postoperative pain
  - Acute pain in the chest, abdomen or back
  - Headache
  - Fractures

Medicines for pain (analgesics)

- Various ways where pharma & non-pharma option can treat pain
- Acute pain is classified either:
  - Minor trauma: strains, sprains, dislocations, fractures, minor chest injuries
  - Major trauma: major chest & head injuries
  - Associated w/ surgery: perioperative pain

Different drugs are used to treat different types of pain:

Drug	Nociceptive	Neuropathic
Paracetamol	Effective, most useful when taking max dose regularly (minimal anti inflame effect)	Less effective
NSAIDs	Effective (useful anti-inflammatory effect)	Less effective
Opioids	Effective	May be effective
Antidepressants (TCA, SSRI) Antipileptics (gabapentin) Local anaesthetics (lidocaine)	Rarely used	May be effective (TCAs & antipileptics are treatment of choice

How analgesics work

~ Opioid analgesics

- Opioids, generaly, mimic the endogenous substances, the endorphins, acton opioid receptors which exist in the brain, spinal cord & the periphery.
- Endorphins = morphine-like substances naturally produced in the body. They all have some opioid core of 5 amino acids

Wide range of functions: regulate heart function, hormone mediator, mood & emotion control. They are thought to be produced under various circumstances in which acute relief of pain or mental distress is required.

- "Endorphins" refer to 3 families of endogenous opioid peptides:
  - Enkephalins (Met-; Leu-)
  - Dynorphins (dyn^{1-17}; dyn^{1-8}; dyn^{1-13})
  - Endorphins (β; α-Neo; β-Neo)

All the endorphins contain the fragment Tyr-Gly-Gly-Phe-(Met/Leu)

→ Key fun interaction w/ opioid receptors

- The phenol of morphine mimics the N-term Tyrosine
- The 3° amine of morphine mimics the 1° amine group of Tyrosine

- Endorphins are release in response to pleasant moment

→ Relieving pain, but can also be addictive

~ Opioid receptors

- 3 main types: μ, δ, K or MOP, DOP, KOP
- Activation of opioid receptors → various effects on the body

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		μ (MOP)	δ (DOP)	κ (KOP)
Analgesia	Brain	+++	−	−
	Spinal	++	++	−
	Peripheral	++	−	++
Respiratory depression		+++	++	−
Pupil constriction		++	−	+
↓GI mobility		++	++	+
Euphoria		+++	−	−
Dysphoria		−	−	+++
Sedation		++	−	++
Physical dependence		+++	−	+

- Some agonists, partial agonists & antagonists

		MOP	DOP	KOP
Naturally occurring agonists	Morphine	+++		+
	Hydromorphone	+++		
Prodrugs	Codein			
	Oxycodone	++		+
Synthetic agonists	Pethidine	+++		+
	Fentanyl	+++		
	Methadone	+++		
Synthetic partial agonist	Buprenorphine	±	−	−
Antagonist	Naloxone	− − −	−	− −
	Naltrexone	− − −	−	− − −
	Methyl naltrexone	− − −	−	− − −

- While codein has no activity at MOP, it can be metabolized into morphine
Oxycodone has week activity at MOP, & is metabolized to various opioids

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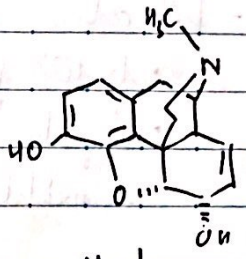
M receptor agonists

- Pharmacophore of MOP agonists:
  - Phenol (associated w/ aromatic ring)
  - Nitrogen atom



Morphine

~ Agonists that are not prodrugs

- They also possess the essential functional group to act at MOP
  Morphine is metabolized to morphine-6-glucuronide which is also a MOP agonist

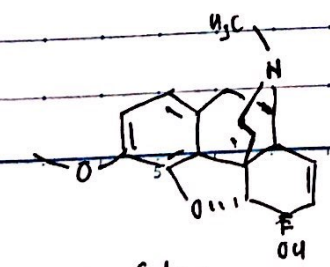
- Opioid receptors are GPCRs that coupled to the G_i protein (inhibitory)
  → Hyperpolarization via various mechanisms { ↓ cAMP; Ca^{2+} channels closed; K^+ channels opened
  → Inhibit action potential propagation

- Although all subtypes of opioid receptors can cause analgesia, MOP are expressed in greater number & in multiple regions → Main target.
  Activation of MOP inhibits the descending pain pathways → Alter pain perception
  Activation of MOP can also inhibit activation of secondary neurons project to the brain & primary neuronal activation that transmit pain signal to spinal cord

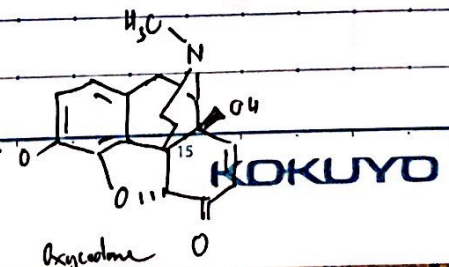
- Side effects are due to activation of opioid receptors that are not associated w/ pain pathways

~ Agonists that are prodrugs

- They need metabolic activity to work
  The ether group instead of phenol ↑ absorption & bioavailability since hydroxyl group can be metabolized quickly → ↓ duration of action



Codeine



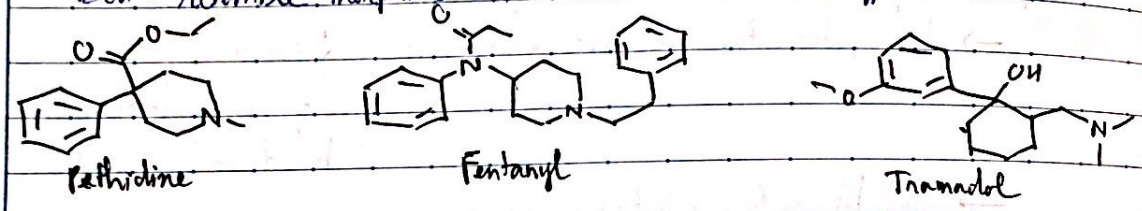
Oxycodone

- Both codeine & oxycodone are often taken orally.
  - 1-10% of codeine is metabolized by CYP2D6 to morphine.
  - Oxycodone is metabolized by many CYPs, including 2D6 & 3A4, to form various metabolites, eg oxymorphone

- Variants of CYP2D6 → reduction in metabolism or ↑ in production
  → Careful when dosing

~ Non-opiate agonists

- Don't resemble morphine → bind to MOR in a different manner.



- Pethidine is no longer use due to the production of metabolite Norpethidine
  → Less analgesic effect but more excitatory CNS effect → anxiety, seizures.
  Pethidine also inhibits reuptake of serotonin into neuron

- Tramadol also inhibit serotonin reuptake
  → Both Pethidine & Tramadol shouldn't be used w/ form SSRI or SNRI to cause serotonine syndrome. (abd cramps, diarrhea, tachycardia, sweating, fever, agitation)

- Fentanyl should also not be used w/ serotonin increasing medicines (block serotonin reuptake but also act on serotonin receptors)
  Fentanyl is highly lipophilic → patch (chronic) & lozenge (palliative pain)
  Fentanyl is contraindicated for opiate-naive patient → only use when other opioids are not help

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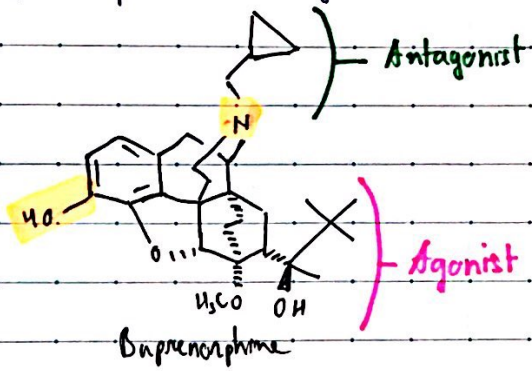
~ Partial agonists

- Buprenorphine is used as analgesic or opioid replacement therapy (ORT)



Buprenorphine

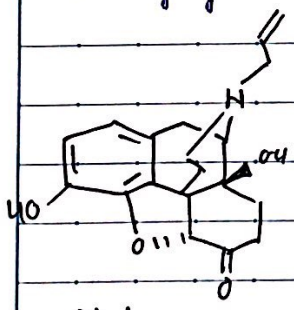
- It has partial agonist activity at MOP but antagonist activity at DOP & KOP
  → Less side effect at higher dose

At higher dose, there is no ↑ in analgesia, but ↑ in suppression of withdrawal symptoms.

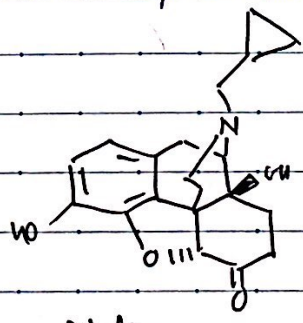
- Despite being a partial agonist, Buprenorphine binds to MOP w/ high affinity.
  → Displace morphine & slowly dissociate from MOP
  → Suppress opioid withdrawal symptoms

~ Antagonists

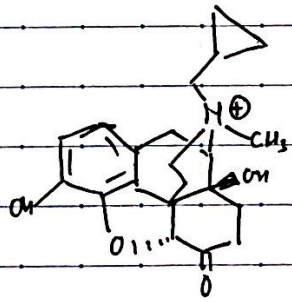
- Used for opioid overdose to ↓ side effects
  Change from N-CH_3 to an N-allyl or an N-cyclopropylmethyl



Naloxone



Naltrexone



- Naloxone is rapidly metabolized → low bioavailability
  → Can be formulated w/ agonists at an appropriate dose
  Eg: Targin = Oxycodone + Naloxone
  • Naloxone doesn't _____ w/ analgesic effect due to low bioavailability
  • Naloxone ↓ constipation since it stays in the gut