L11: Multiple system (Immunosuppression, toxicology and other noteworthy drugs)

IMMUNUOSUPPRESSANTS - GLUCOCORTICOID PHARMACOLOGY

PATHO REVIEW

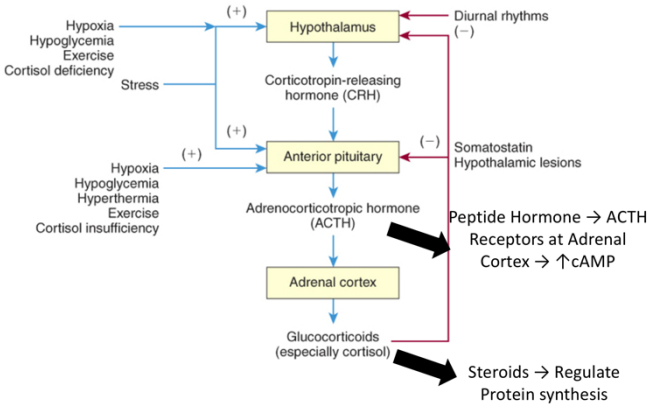
Adrenal Glands

2 Glands-in-1

- Cortex → Glucocorticoids, Mineralocorticoids & a bit of Estrogen & Testosterone
  - Zona Fasciculata → Glucocorticoids → Cortisol
  - Zona Glomerulosa → Mineralocorticoids → Aldosterone
- Medulla → Epinephrine (Adrenaline) & Norepinephrine

Glucocorticoids (GCC)

IMPORTANT TO UNDERSTAND PATHWAY



<u>Main regulators</u>

- Cortisol Levels
- Stress
- Diurnal Rhythms

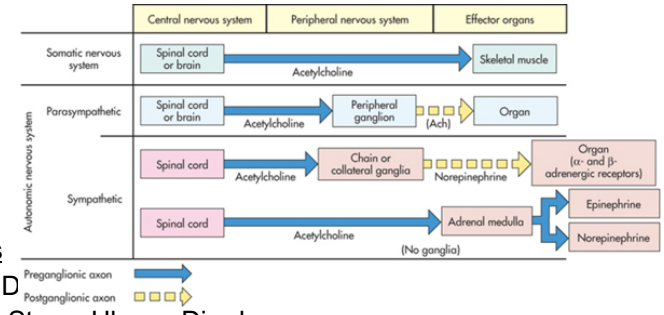
<u>Main effects</u>

- ↑ Blood glucose
- ↑ Glycogen and protein catabolism
- ↑ Neuronal functions
- Powerful anti-inflammatory
- Anti-growth (+ ↓ bone deposition)

Adrenal Medulla

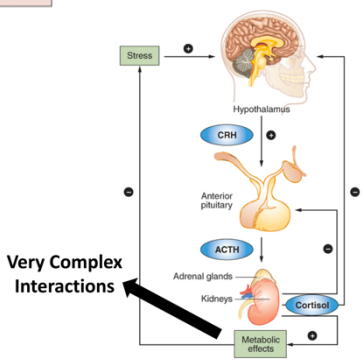
- Neuroendocrine Sympathetic System
  - Pheochromocytomas store & release Epi/NE

- Endocrine Catecholamines → Promote Hyperglycemia
  - ↑ Immune Response & Skeletal Muscle Power → Response to Stress
  - Inhibition of Reproduction & Growth → Energy Preservation



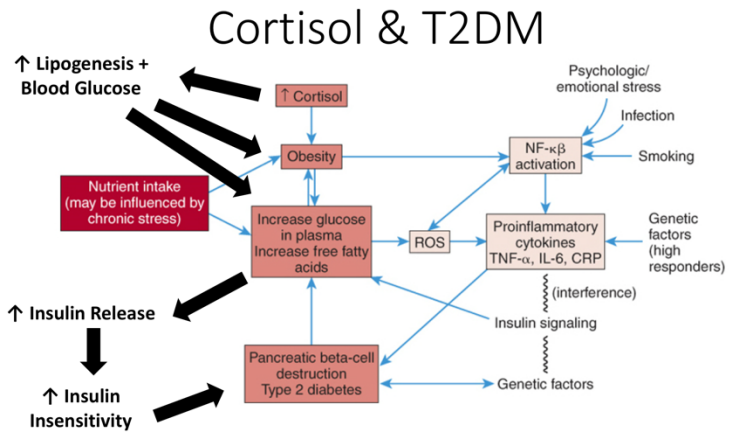
<u>Stress related disorders</u>

- Cardiovascular D
- GI Disorders → Stress Ulcers; Diarrhea
- Urinary System → Diuresis (Bathroom stress!)
- Muscle & Connective Tissues → Rheumatoid Arthritis
- Skin & Bone → Eczema; Acne; Osteoporosis
- Pulmonary Disorders → Asthma (Hypersensitivity Reaction)
- Endocrine Disorders → Type-II Diabetes



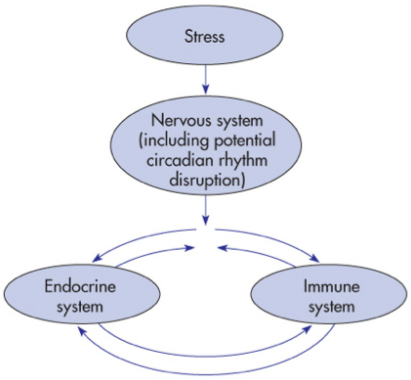
- CNS Disorders → Depression; Fatigue
- Immune Diseases → Immunosuppression

Cortisol and T2DM



Cortisol & Female Reproduction

- Cortisol inhibits Female Reproductive System
- Estrogen concentration variations → ↑ Vulnerability
    - Mood Alterations
    - Eating Disorders
    - Auto-Immune Diseases



Stress & Immunity

<u>Acute Stress = Beneficial effect</u>

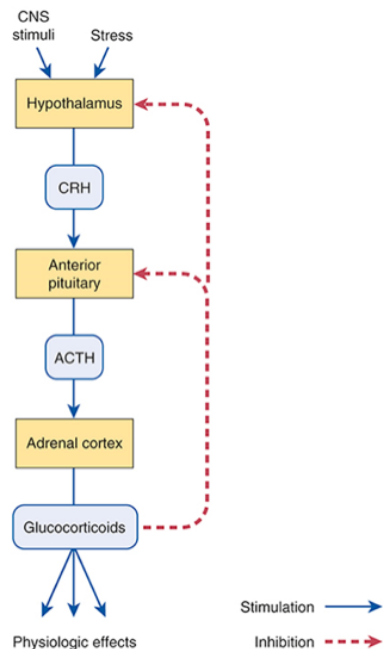
- Inhibits initial inflammatory effects → ↓ Pain Sensitivity
- Promotes resolution and repair

<u>Chronic stress = harmful effects</u>

- Th1 to Th2 shift → Immunosuppression
- ↑ Risk of Allergic Reactions & Infections
- ↑ Risk of several other diseases (Ex.: T2DM; Cancer; Cardiovascular Diseases)

Cortisol & Immunity

Boost Th2/Humoral Responses → ↑ Risk of Acute Allergic Reaction → Inhibits Th1/Cellular Responses & Innate Immunity → Therapeutically used as powerful immunosuppressive agents (ex.: Anti-Graft Rejections)



BACK TO PHARM

Glucocorticoid Pharmacology

Systemic Glucocorticoids: Half-Lives, Relative Potencies, and Equivalent Doses

Drug	Biologic Half-Life (hr)	Relative Mineralocorticoid Potency[a]	Relative Glucocorticoid (Anti-Inflammatory) Potency[b]	Equivalent Anti-Inflammatory Dose (mg)[c]
SHORT ACTING				
Cortisone	8–12	2	0.8	25
Hydrocortisone	8–12	2	1	20
INTERMEDIATE ACTING				
Prednisolone	18–36	1	4	5
Prednisone	18–36	1	4	5
Methylprednisolone	18–36	0	5	4
Triamcinolone	18–36	0	5	4
LONG ACTING				
Betamethasone	36–54	0	20–30	0.75
Dexamethasone	36–54	0	20–30	0.75

- Dividing into 3 categories: short, intermediate, long acting (duration)
- **Know 1 drug per class (Cortisone, prednisone, dexamethasone)**

Relative mineralocorticoid potency
- Ability of the hormone/drug to have aldosterone-like actions
- Remember, aldosterone is mostly important for fluid retention, whereas cortisol is important to induce catabolism (breakdown of protein/fat for energy as part of the stress response)
    - Number is relative → 2 = twice the action of 1 VS 0 = no action at all

Relative glucocorticoid (anti-inflammatory) potency
- Anti-inflammatory/immunosuppression actions
    - Nb = relative → hydrocortisone (baseline), cortisol (80% as effective as hydrocortisone)

Equivalent anti-inflammatory dose
- Example of **hydrocortisone VS Prednisone**
    - Anti-inflammatory potency (1) → equivalent anti-inflammatory dose (5 mg)
    - Anti-inflammatory potency (4) → equivalent anti-inflammatory dose (5x4=20 mg)
        - This explains the different doses of each GCC

Dosage and administration

Choice of GCC
- Biologic half-life = Time to leave body tissues → **More representative than plasma half-life for GCC**
- Avoid GCC with high mineralocorticoid (fluid retention) potency
    - Bcs too much fluid retention can lead to another problem to deal with

Admin
- Multiple routes: Oral, parenteral, topical, inhalational, etc.
- Admin before 9AM = Optimal → Mimics circadian rhythm of secretion
    - We have high levels of GCC in the AM
- Esters used in preparations determines biological duration of action

Dosage guidelines
- Individualised via trial & error
- High-dose prolonged therapy **only if** 1) Life-threatening or 2) Potential for permanent disability
    - Bcs too much toxicity long term

Alternate-day therapy = intermediate-acting GCC every other days
- Advantages: ↓ Adrenal Suppression risk + Growth delay & Overall toxicity
- Drawback: You could have symptom flare-up on the non-dosing day (every 2nd day)

Therapeutic uses → mostly inflammatory related disease

Pathology	Comments
Rheumatoid Arthritis	Adjuvant during acute symptom exacerbations Local injections whenever possible → ↑ Efficacy + ↓ Toxicity
Systemic Lupus Erythematosus	Agressive short-term high-dose glucocorticoid = Best for Sx management
Inflammatory Bowel Disease	Only vs. Severe UC or CD
Asthma & Allergies	Inhaled GCC = Best antiasthma medication Delayed onset → Inefficient against anaphylaxis
Dermatologic Disorders	Topical administration limits toxicity
Cancer	Mostly blood-borne cancers (ex.: Lymphomas & Leukemias)
Allograft Rejection Prevention	Discussed in the next few slides Initiated at surgery and continued indefinitely
Preterm Respiratory Distress Syndrome Prevention	GCC necessary for fetal lung maturation Dexamethasone injections to mothers before pre-term delivery ↓ likelihood of respiratory distress in the newborn

Adverse effects

- Intensity **mostly dependent on therapy duration** / Only a little by dose size

Toxicity	Comments
Adrenal Insufficiency	See next slide for Management
Osteoporosis	↓ Osteoblast activity + ↓ Ca^{2+} absorption → Hypocalcemia Hypocalcemia → PTH → ↑ Osteoclast activity
Infection	↑ new infection risk + ↑ latent reactivation (ex.: TB or HSV) Special prophylaxis against Pneumocystis pneumonia
Glucose Intolerance	↑ Blood glucose levels → Exacerbation of diabetic symptoms
Psychological Disturbances	From insomnia/anxiety to hallucinations and delirium Type of disturbance depends on duration and dosing Independent of good psychological health or history of mental illness Sx can be managed and resolved once GCC is discontinued
Other important toxicities	Peptic Ulcers → Via Prostaglandin inhibition Cushing-like Syndrome/ Growth delay in children Cataracts & Glaucoma / Fluid & Electrolyte imbalance exacerbation

<u>Long-term use</u>

- High dose, short time = less harmful than low dose and long time
  - GCC present for a long time = body thinks the body has other means to produce GCC = shuts down the pathway!!
  - Leads to adrenal insufficiency
    - Pathway shut down = adrenal glands stop receiving message = stop working

Interactions & Contraindications

Situation	Comments
Pregnancy	Risk of fetal adrenal hypoplasia → Not contraindicated but monitor frequently
Lactation	Enters breast milk → May cause growth delay - Lipid soluble enters breast milk
Hypokalemia	Careful when combined with other potassium-loss promoting RX (Digoxin & Diuretics) - Related to aldosterone-like action
Other Interactions	NSAIDs → ↑ Peptic Ulcers & GI Bleeding - GCC + NSAIDS = peptic ulcers risk → combination of effects Must increase dosage of Insulin & Hypoglycemics - Bcs hyperglycemia effect of GCC Vaccines → Decreased efficacy due to immunosuppression - Necessary to have a good immune response to give vaccine. If immunosuppressed from GCC, that weakened virus from the vaccine can make you sick
Contraindications	Live virus vaccines & systemic fungal infections
Precautions	Anyone at risk of one of the toxicities or interactions mentioned
Specific Toxicity: Adrenal Supression	Development: Via excessive negative feedback → Adrenal atrophy - Adrenal atrophy d/t shut down adreanal pathway Management: Must ↑ GCC dosage during times of stress - Levels of cortisol are good for every day situation, but when you have a stressful event (ex. Seeing a bear), your adrenal can't produce that cortisol boost. Strict and long withdrawal schedule = tapering - If you stop taking GCC, it would take time for the adrenal glands to start again.. Need to taper it off gradually so that the decrease in concentration slowly kick starts the adrenal gland (forces you to prolong the duration of drug use = higher risk of side effects).

IMMUNOSUPRESSION

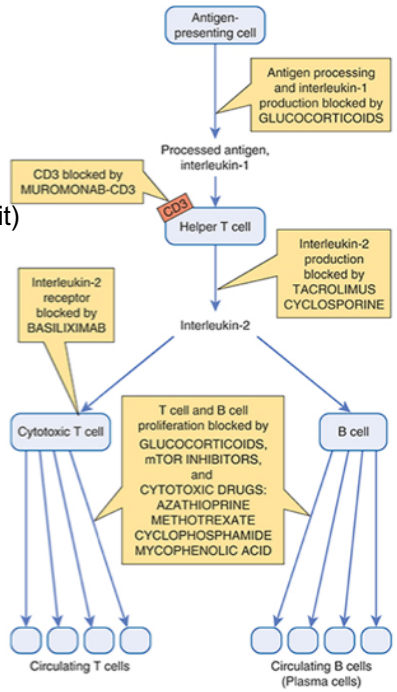
Principal indications

1) Autoimmune distort treatment
2) Graft VS host disease (GvHD) prevention
   Graft versus host disease **(GvHD) → rejection**
   - the immune system recognizes it as foreign and tries to destroy it)
   - Graft prevention therapy is lifelong & always toxic

Main toxicities

1) Increased risk of infections
   - Risk/benefit: infections can be managed with prevention, abx versus dying from organ failure
2) Increased risk of cancer

Good review (image) →



Glucocorticoids

- Prednisone = Common choice for graft rejection prevention

- Very large dosage → High toxicity over time
    - Keep the drug for the rest of your life bcs body always consider the organ as foreign
- AE almost guaranteed to develop at a certain time.: Osteoporosis / ↑ Infections / Adrenal suppression

Indications:

- Graft rejection prevention
- Asthma Tx
- Autoimmune management (ex: rheumatoid arthritis)

Immunosuppressive actions:

See summary image → effect directly on the WBCs (circulating T cells or B cells)

IL-2 is important for the activation of T/B cells

- ↑ Leukocyte apoptosis + ↓ proliferation
- ↓ IL-2 synthesis by macrophages & lymphocytes
- ↓ IL-1 sensitivity of T-Lymphocytes
    - T-lymphocytes = most responsible for the organ rejection problem

Cyclosporine + Tacrolimus → Both are the BEST drugs available for organ rejection prevention.

Calcineurin Inhibitors: Cyclosporine

MOA

- ↓ IL-2 → ↓ B & T-Cell proliferation
    - Gets inside the cell and forms a complex that blocks the action of calcineurin → Calcineurin activates the transcription factor (NFTK) which is responsible for making IL-2→ Block IL-2 synthesis
- No bone marrow suppression

Kinetics

- PO preferred over IV
- 90-98% plasma protein-bound
- CYP3A4 metabolism
- Bile excretion / Practically not found in urine
    - Pretty special!!

Serious AE

- Kidney damage & Infections in 75% of patients = almost certain
- Neprhotoxicity →↓ renal blood flow & GFR
- Monitor blood urea nitrogen & serum creatinine
- Infections → Monitor for fever & sore throat

Interactions:

- CYP3A4 inducers (ex.: phenytoin) can ↑ GvHD
- CYP3A4 inhibitors (ex.: ketoconazole) ↑ Toxicity
- Ketoconazole given on purpose to ↓ cost of Tx
    - Ketoconazole inhibits CYP3A4
    - Given purposely so we don't have to give high doses = same result but less drug given
- Nephrotoxic Rx (ex.: Aminoglycosides)
- Grapefruit juice → CYP3A4 inhibitor

**Dosage should be adjusted based on nephrotoxicity & cyclosporine trough levels*

Calcineurin Inhibitors: Tacrolimus

Action & Kinetics:

- Same as Cyclosporine

Comparison with Cyclosporine for GvHD:

- Less acute graft rejection episodes
- More narrow therapeutic index → less adherence
- A bit more effective than cyclosporine

Serious Adverse Effects:

- Neprhotoxicity in 33-40% of patients
- Infections → Monitor for fever & sore throat
- Anaphylaxis reaction with IV injections

Interactions:

- CYP3A4 inducers & inhibitors
- NSAIDs → ↑ Kidney damage

Dosage should be adjusted based on nephrotoxicity & Tacrolimus trough levels

Cytotoxic Agents: Mycophenolate Mofetil (MMF)

- Discussed in the cancer pharmacology lecture: Methotrexate / Azathiopurine / Cyclophosphamide
- Lower dosage than chemotherapy
- Non-specific killing of proliferating cells

MOA

- MMF is the exception from other cytotoxic agents
  - Specific B & T-lymphocyte killing
  - Not just killing all the rapidly dividing cells
- Inhibits inosine monophosphate dehydrogenase (necessary for the synthesis of nucleic acid) = can't produce the DNA molecules to replicate
- Depend on De Novo purine synthesis

Usage

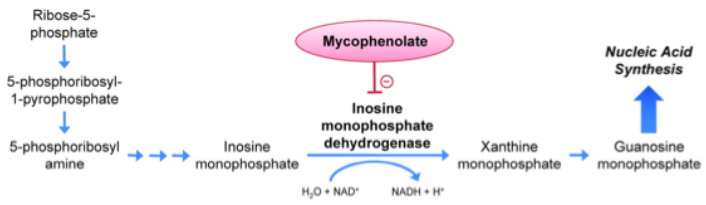
- GvHD prevention when combined with GCC or Cyclopsorine
  - Rarely use this medication on its own

AE

- High Toxicity → ex.: Myelosuppression / GI disturbances / Alopecia
- Adverse Effects: Nausea / Vomiting / Severe Neutropenia / ↑ Cancer risk

Interactions

- Antacids & Cholestyramine ↓ MMF absorption



Monoclonal Antibodies – Muromonab (Anti-CD3)

Action:

- Block T-Cell function
    - Blocks CD3 located on the helper T-cell
- ↓ Lymphocyte activation & proliferation

Uses: GvHD prevention

Adverse Effects:

- Fever / Chest pain / Nausea + Vomiting → Decrease over time
- **Potential fatal anaphylactic reactions**

Kinetics

- MUST BE ADMIN IV → Not PO bcs mAbs are proteins = gastric acid will completely dissolve them

Monoclonal antibodies – Basiliximab (Anti-IL-2)

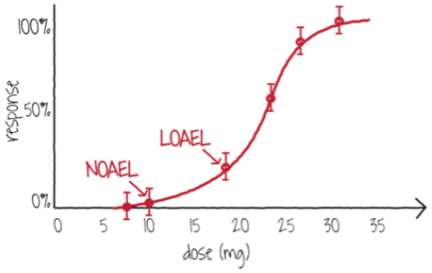
Action

- IL-2 receptor blocker = block T-Cell activation

Use : GvHD prophylaxis post-renal transplant only

Adverse effects

- Tolerated: no infection or cancer ↑ risk
- Rare anaphylaxis reactions



POISONING MANAGEMENT

Principles of Toxicology

- The science of poison and adverse effects/toxicity
- Interested in risk factors and exposure to certain chemicals

NOEL: no observable effect level vs LOEL: Lowest Observed Effect Level

When you tested this substance, when you gave 10mg, you didn't notice any toxicity. But when you gave 18mg, you observed toxicity. And the more you give, the more toxicity you have. So before 18mg, the drug does not produce any significant AE.

Relative Risk (RR)

- What is the incidence of Post-Traumatic Stress (PTS) in the normal population versus those who suffered a severe Traumatic Brain Injury (TBI)?

$$Relative\ Risk\ (RR) = \frac{Event\ Incidence\ in\ a\ Population\ Exposed\ to\ Risk\ Factor}{Event\ Incidence\ in\ Unexposed\ Population}$$

Groups	PTS	No PTS	Total
No TBI	10	990	1000
sTBI	172	828	1000

Example: RR sTBI = (172/1000) / (10/1000) = 0.172 / 0.01 = 17.2

Conclusion: Severe TBI increases risk of suffering of PTS by 17.2 times relative to having no TBI

- Always compare to the healthy population

RR when you know what the person has been exposed to but you don't know the consequences
RR you knew who had a PTS, you don't know who had TBI
RR compare a smoker to a non-smoker

Odds Ratio (OR)

OR: you know the consequence, you just don't know what they have been exposed to.
OR: you dont know who has a TBI, you know who had PTS
OR: compare 2 smokers together, but one had lung cancer and the other didnt.

Odds Ratio (cont'd)

- When you don't know the incidence of the outcome of interest in a case-control study
- What is the probability of having sustained (exposed to) a Traumatic Brain Injury (TBI) among those who suffer from Post-Traumatic Stress (PTS) ?

$$Odds\ Ratio\ (OR) = \frac{Odds\ that\ a\ case\ was\ exposed\ to\ a\ risk\ factor}{Odds\ that\ a\ control\ was\ exposed\ to\ a\ risk\ factor}$$

Groups	PTS	No PTS	Total
No TBI	10	990	1000
TBI	216	2784	3000

Example.: OR sTBI = (216/10) / (2784/990) = 21.6 / 2.812 = 7.68
Conclusion: Individuals with PTS are 7.68 times more likely to have suffered a TBI than those without PTS

What's poisoning?

- Pathologic state caused by a toxic agent
- Cause: Intentional or accidental
- Sx often mimcs those of diseases → always consider this option...
    - Whenever someone is sick, poisoning should always be one of the potential possibilites.
- Incidence highest in children but lowest mortality
    - Kids put everything in their mouth but mortaility rate is usually less than adults
- US 2014 data: 95% of poisoning deaths = Drug-related / 75% of suicides

Fundamentals of Treatment

1) Supportive Care
    - Poison independent
    - Ex: Respiratory support
    - Ex: Fluid & pH imbalances management
    - Ex: Blood Glucose monitoring

2) Poison identification
    - Best = Sequential blood samples 2h apart

While blood is being analyzed, you want to inhibit/limit absorption of, so if a substance was injected, use activated charcoal or gastric lavage.

3) Inhibit further absorption
    - Ingested → Activated charcoal / gastric lavage
    - Topical → Surface decontamination / showering

Once you stop absorption, try to get it out, clean body

4) Promote poison excretion
    - Diuretics
    - Hemodyalysis
    - Blood exchange

5) Antidote if available → once the toxic agent has been identified
    - Ex.: Nalaxone for opioids
    - Rare / most poisons have no antidotes

Activated Charcoal → minimizing poison absorption

- Preferred method
- Inert and unabsorbed → Very safe
- Charcoal-poison complex = Eliminated in stool → Turns black!

MOA

- Stays in GIT, binds to other substances → charcoal + substances attached don't get absorbed → excreted → black stool

Efficiency

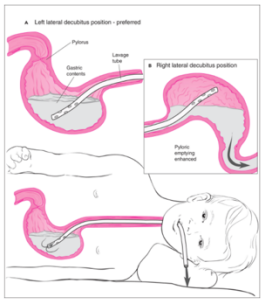
- 90% efficient within 30mins
- Only 37% efficient within 60mins

Usage

- Agents well absorbed by activated charcoal (aspirin, benzo, beta-blocker, furosemides, NSAIDS, atropine...)
- Agents poorly absorbed by activated charcoal (cyanide, ethanol, ethylene glycol, iron, isopropanol, lithium, methanol. Strong mineral acids & alkali)

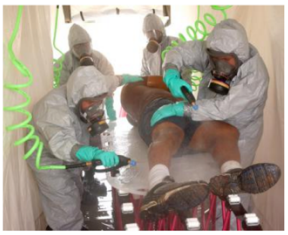
Other approaches to minimize poison absorption

Gastric Lavage



Whole-Bowel Irrigation

Body surface decontamination



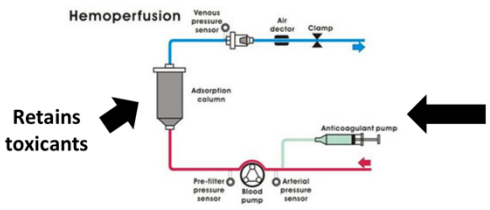
Maximizing Poison Removal

- Drugs ↑ Excretion: Sodium Bicarbonate
- Makes urine alkaline
- Acids become polar → Trapped in the tubules
- ↓ reabsorption of acids (ex.: aspirin, phenobarbital)

Drug\Environment	Acidic	Alkaline
Strong Acid	Polar/Ionized	
Weak Acid	**Non-Polar/Unionized**	**Polar/Ionized**
Weak Base	**Polar/Ionized**	**Non-Polar/Unionized**
Strong Base	Polar/Ionized	

Ion trapping

- Ion trapping: depending on pH and the ionization of the molecules → stays on one side of the membrane or the other
  - If you want to get things out of the body, you're thinking aobut your kidneys (you want to minimize the reabsorption of the molecules)
  - provide sodium bicarbonate (bcs most drugs are acidic) to make the urine alkaline → by doing this, most of the weak acid become POLAR and when you're polar, you DONT cross the membrane, so you stay in the urine and you get out!.
  - In the case of alkaline drugs, try to make the urine acidic.



Nondrug procedures
Ex.: Hemodyalysis / Hemoperfusion
Best when blood toxicants levels are high + poor binding to plasma proteins

Hemodialysis
Special compartment that retain all the toxic molecules & then put blood back into the system

Specific Antidotes

Specific Antidotes Discussed in Other Chapters

Antidote		Toxic/Overdosed Substance	Chapter
Generic Name	Brand Name		
Atropine		Muscarinic agonists, cholinesterase inhibitors	14
Physostigmine		Anticholinergic drugs	15
Neostigmine	Prostigmin	Nondepolarizing neuromuscular blockers	15
Pralidoxime	Protopam	Organophosphate cholinesterase inhibitors	15
Naloxone	Narcan	Opioids	28
Flumazenil	Romazicon	Benzodiazepines	34
Digoxin immune Fab	Digibind	Digoxin, digitoxin	48
Vitamin K		Warfarin	52
Protamine sulfate		Heparin	52
Idarucizumab	Praxbind	Dabigatran	52
Glucagon		Insulin-induced hypoglycemia	57
Acetylcysteine	Mucomyst	Acetaminophen	71
Leucovorin		Methotrexate and other folate antagonists	102
Pentetate calcium trisodium		Radioactive plutonium, americium, or curium	110
Pentetate zinc trisodium		Radioactive plutonium, americium, or curium	110
Prussian blue	Radiogardase	Radioactive cesium-137 and nonradioactive thallium	110
Potassium iodide	ThyroShield	Radioactive iodine	110

Some antidotes to specific drugs. Most have been discussed in class

- Vit K (warfarin), Glucagon (insulin induced hypoglycemia), leucovorin (high dose of MTX then give the antidote to kill CA cells and save healthy cells) Atropine (muscarinic agonist)

Heavy Metal Antagonists

- Chelating Agents: Inhibit metal ion absorption
    - Binds to a molecule and prevents it from doing anything (not receptor-binding, rather it's molecule-binding)

Good properties:

- High affinity for metal ions / Low affinity for everything else
- Easily excretable / Formation of less toxic complexes

Deferoxamine

Usage

- Iron poisoning-specific antidote
- Does not affect iron in hemoglobin

Indications

- Parenteral administration / Kidney excretion

Toxicity:

- Common: Injection-site reactions / Fever
- Rapid infusion: Tachycardia or hypotension
- Prolonged infusion: Allergic reactions & GI discomfort

Dimercaprol

- Chelates: Arsenic / Gold / Mercury / Lead
- Greatest benefits when administered early

Indications

- Deep IM injections / Kidney excretion

Toxicity:

- Common: Tachycardia & Hypertension
- Dissociation at acidic pH: Acidic urine → Nephrotoxicity
    - If urine is acid, would dissociate the ions in the urine only = accumulates in kidney = nephrotoxicity
- Made from peanut oil → Allergies!!

Food Poisoning

Common sources: Raw eggs, meat & fish, Salads, Unpasturized milk
Common pathogen: Salmonella, E.Coli, Rotavirus

Complications:
- Dehydration
- Possible kidney failure with certain strands of E.Coli

Management
- Usually only 1 day or 2. Not much to do
- Best thing = prevention
- Make sure you're hydrated + electrolytes balanced + rest

DRUGS AS WEAPON – CHEMICAL TERRORISM

History Capsule
- Ancient Greece: Hercules using **Hydra poison on arrows** = 1st account of chemical warfare
- Early Modern Era: Da Vinci proposed to throw **arsenic poison fumes** at enemy ships
- 1899 Hague Conference: Proposal to ban use of '**shells filled with asphyxiating gas**' passed
- WW1 said Yes but No…: 124k tons of gas produced by the end of the war
  - 1st **usage of Mustard Gas** (1st anticancer Rx)
- 1925: Geneva Protocol ratification → Nations vow to never use chemical gas in warfare
- WW2: Jewish Holocaust but no usage during combat by allies or Germany…
- Post WW2: Used on several occasions in middle east conflicts
  - Most recently in the Syrian Civil War (**Sarin & mustard gas**)

Anthrax
- Aerobic Gram+ Baccili
- Survives for decades as dormant spores
- Activated by presence of nutrients
  - Can survive until It finds the right location to grow → activated by presence of nutrients (good pH, glucose, moisture) → usually on human

Transmission
- Transmission: Inhalational or Cutaneous
- NOT person-to-person

Inhalational Anthrax:
- Bacterial toxin → causes hemorrhage + Edema + Necrosis
- 2-6 days: Initial symptoms are mild
- Few days later: Severe sudden septicimia & respiratory distress
- Death is inevitable once toxin levels reach a critical threshold
- Fatality rate >80%

Cutaneous Anthrax:
- Onset of symptoms within 1-7 days
- Formation of scab-like/coal-like lesion = **characteristics**
- Only life-threatening of systemic infection develops
  - Affects skin rather than airways. Less fatal than inhalation anthrax

Treatment

Therapy of Inhalational Anthrax in the Mass Casualty Setting

Patient Group	Preferred Initial Oral Therapy	Alternative Oral Therapy (If Strain Is Proved Susceptible)	Duration
Adults	Ciprofloxacin, 500 mg every 12 hr	Doxycycline, 100 mg every 12 hr Amoxicillin, 500 mg every 8 hr	60 days
Children	Ciprofloxacin, 10–15 mg every 12 hr, but no more than 1 gm/day	≥20 kg: amoxicillin, 500 mg every 8 hr <20 kg: amoxicillin, 13.3 mg/kg every 8 hr	60 days
Pregnant	Ciprofloxacin, 500 mg every 12 hr	Amoxicillin, 500 mg every 8 hr	60 days

- Initiation with IV Ciprofloxacin is best but not practical for mass casualties
    - If allergic reaction or rx resistance, use other options (amoxicillin)
- mABs & IV Anthrax Immunoglobulins: Neutralize toxins → limit damage post-infection
    - Monoclonal Abs and IV immunoglobulins can neutralize toxins. However, they only limit the damage (can be given quickly unti proper medicaiton).
- Cutaneous Anthrax TX: Same as Table above. Prevents systemic infection but not skin lesions

History Capsule : 2001 US Anthrax Attack

- 5 Letters with anthrax sent to news media & 2 democratic senators. When they opened the letter, target + other ppl around them inhaled Anthrax → 22 affected/5 died
- Motive: Saving the Anthrax vaccination program → It worked…

Smallpox

- Use smallpox virus as biochemical terrorism
    - Irony: Smallpox eradicated from the planet in 1977 → Vaccination programs stopped in 1982. Means that now it could be used by biochemical terrorist and no one is protected…
- Vaccine = Only treatment available
    - Military personnel have mandatory vaccination since 2003
    - Vaccination is not recommended for civilians at this point
    - In the event of a terrorist attack immunization would be provided
- New reasearch with antiviral drugs suggest some could be beneficial
- Symptoms: High fever / Bumpy & fluid filled skin rash
- Mortality ≈ 30%

Transmission:

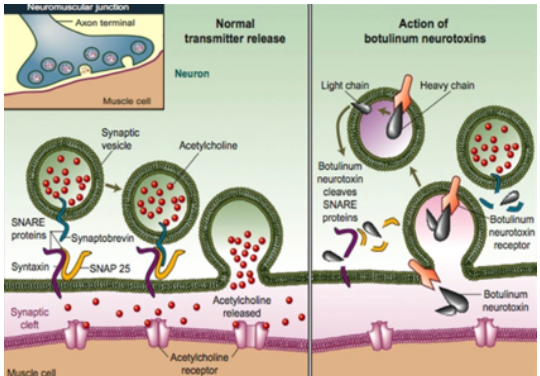
- Very virulent & contagious person-to-person → Cough & sneezes
- Also possible via contaminated clothing/bedding
- Most contagious during skin scab & rash phase

Botulinum Toxin

- Most potent poison known, 1g can kill 1 million people!!
    - The number 1 most potent poison known in the world. The substance which you need to give the smallest amount to kill someone

MOA

- Inhibits cholinergic transmission at neuromuscular junction and autonomous nervous system neurons
- Ach needs to bind to the snare proteins to get the vesicle to unfuse and dump the Ach for its propagation



- Botox breaks down the anchors, so that the next vesicles cannot anchor and dump Ach in the junction = muscle is pa ralyzed bcs Ach is trappe

Symptoms
- Symptoms of poisoning ≈ Myasthenia Gravis
- Progressive top-down paralysis
- Eyelid droop, difficulty swallowing
- Muscle weakness & severe fatigue
- Death: Respiratory muscle paralysis

Treatment
- Supportive Care + Antidote infusion
- Antitoxin can limit damage but not reverse it
    - Antitoxin can protect the anchors that are still there but cannot replace the anchors broken down
- Takes several months to restore transmission. Hence botox injections every couple of months

Ricin
- Toxin found in castor beans
    - Castor oil is very valuable for food, medecine and other products but needs to be separated from the ricin component!

MOA
- Ribosome inhibition
    - It inhibits the funciton of ribosomes (those that make the protein synthesis from the mRNA).
- ↓ Protein synthesis → Death
    - Can lead to death if you're not producing the proteins for cell function.

Symptoms → depend on route of exposure
- Inhalation:
    - Breathing difficulty & chest pain within hours
    - Cyanosis & death soon follows
    - Fatality depends on concentration inhaled
- Ingestion:
    - Gastric & intestinal hemorrhage
    - Vomiting + Bloody diarrhea
    - Potential kidney, liver & spleen failure
    - Ingestion fatal → Death in 10-12 days

Treatment:
- Supportive Care only
- No antidote available
- Vaccine under development

Nerve Agents
MOA
- Irreversible/Organophosphate Cholinesterse Inhibitors
    - Cholineesterese inhbitors (cholinesterase: breakdown ach). By inhibitng those proteins, Ach sticks around in the neuromuscular juction = over activation = depletion.
- Cause cholinergic crisis

    - Excessive muscarinic action & neuromuscular blockade

Symptoms: DUMBBELS
- Diarrhea, urination, miosis, bradycardia, bronchospasms, emesis, lacrimation, salivation

Treatments
- Mechanical ventilation support
- Atropine to decrease muscarinic activity
    - antidote
- Pralidoxime (organophosphate antidote)
- Diazepam to decrease convulsions

Mustard Gas
- Also known as alkalyting agents when used as anticancer Rx
- Vaporised or spread in water sewage
- Causes severe damage but low fatality → Only 5% of exposed soldiers died during WW1

Symptoms
- depend on tissue exposed & dose
- Delayed onset (2-24h) & usually resolved within few days
    - **Skin:** Swelling & blisters
    - **Eyes:** Very sensitive → Necrosis & Blindness
    - **Respiratory tract:** Hemorrhage → Coughing blood
    - **GI Tract:** Vomiting + Diarrhea
    - **Bone Marrow Supression:** Think anticancer toxicity

Management
- Undress immediately & wash 3x with soap water
- Irrigation of severe skin burns & eyes
- Topical antibiotics & opioid analgesisc PRN

Radiologic Weapons: Nuclear Bomb
- Direct thermal damage vs. Delayed ionizing radiation
    - Exposed to radiation that eminated from the bomb
    - Direct thermal = heat of the explorsion
    - Delayed ionizing radation = suffering from the radiation exposure
- **Acute Radiation Syndrome** develops over weeks
- ↑ risk of cancers (especially blood cancers)
- Radioactive iodine-131 → ↑ Thyroid cancer risk

Acute Radiation Syndrome Sx
- Vomiting & Diarrhea, GI Ulceration, inflammation & Severe burns

Radiation Emergencies Agents

Potassium iodide = radioactive iodide-131 antidote
- Protects thyroid gland
- Efficacy: 100% pre-exposure, 80% within 2h, 40% within 8 hours, 7% within 24h

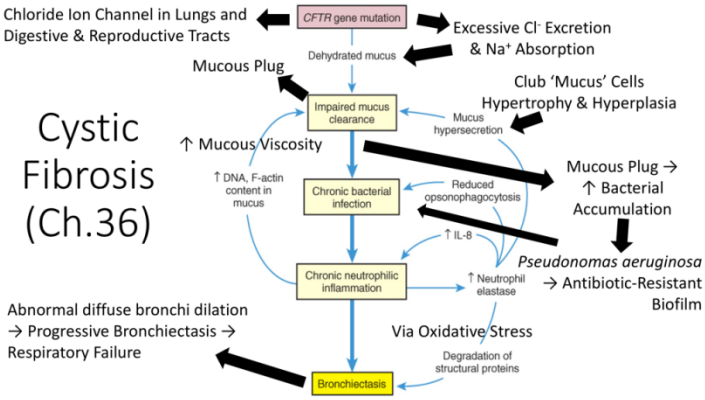
Plutonium Chelator = plutonium/uranium

- IV admin is best
- Efficacy: time-dependent, not 100% effective but better than no tx

MISCELLANEOUS DRUGS

CYSTIC FIBROSIS (CF)

Pathophysiology



Specific Considerations of CF

Pancreas (mutation in the CFTR)

- ↓ Bicarbonate & Digestive Enzymes secretion
- Malabsoprtion Syndrome
- Accumulation of pancreatic enzymes = Cell destruction
- Used to be major CF cause of death

Reproductive organs

- Infertility: 98% of males / 70-80% of females
- Males: Obstruction of vas deferens
- Females: Thick & sticky cervical mucus

Lungs

- Airway plugs & Chronic bacterial colonization = Chronic bronchitis = Progressive lung destruction
- Cause of death for 95% of patients

Drug therapy

- No cure / Only slow disease progression
- Lifespan in 1960s ≈ 5yo VS Lifespan today ≈ 37yo

CF Mangement: CFTR Modifiers: **Ivacaftor & Lumacaftor/Ivacaftor**

- Restores functioning of some of the mutated CFTR proteins
- Very effective & hopes of further development
- Use drugs in combination
    - Allows for a bigger % of people to respond to the dru

MOA

- Abnormal CFTR proteins are constantly closed in CF pts. With drugs, can artificially open CFTR
    - Only works for a subset of CF pts. Seems to be dependent on the type of receptor

Adverse Effects:

- Common: GI manifestations & shortness of breath

- Serious:
    - Hepatotoxicity → Monitor liver enzymes
    - Hypertension → Individualised management
    - Cataract→ Frequent ophtalmologic assessements
- Many interactions with PO medicatiosns

Cost of therapy:

- 512$/dose for children & 1536$/dose in adults
- Usual course of treatment is 2 doses/day
- Several access programs available

CF management: nutritional drugs

- ↓ impact of malabsorption syndrome
- Explains why now CF is considered more a respiratory disease than a digestive disorder
    - Vit. A & E deficiencies are common
    - Vit. D & K deficiencies are rare
    - Supplement all four since safe and cheap

CF management: pulmonary drugs

Drugs	Comments
Inhaled antibiotics for chronic suppressive therapy (part of the disease d/t bacteria in airway)	**Tobramycin (Aminoglycoside) or Aztreonam (penicillin derivative)** Main ADRs: Cough & wheezing No severe systemic toxicity (ex.: Hearing loss) Aztreonam More effective & convenient
PO or IV antibiotics for acute therapy	PO for mild infections / IV for severe Rx of choice: **Aminoglycosides or Penicillin/Clavulanate**
Inhaled Dornase Alfa (unclog airway)	↓ sputum viscosity → ↑ respiratory functions Must be administred daily for life → ≈ 12k$/year
Oral Ibuprofen (decrease inf)	↓ inflammation can slow down disease progression
Inhaled Beta-2 Agonists	Bronchodilators → Review asthma medications

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- Disease of both Upper & Lower Motor Neurons
- Mostly sporadic 5-10% familial
- Super Oxide Dismutase gene (SOD1) mutation = Most common

Pathophysiology = Unclear

- Upper & Lower motor neuron degeneration → Sclerosis (Scarring) of corticospinal tract
- SOD1 ↓ ROS concentrations → Thus neuron damage potentially linked to ↑ ROS
- Accumulation of Ubiquitin in surviving neurons
- Progressive denervation of motor units → Muscular atrophy → Weakness → Paralysis
- Sprouting lower neurons → Insufficient Compensation

- Respiratory failure within 3-5 years…. With some exceptions!!!!

ALS Therapy: Riluzole

Modest benefits (almost unexistant...)

- Glutamate Na^+ channel antagonist
- Only works if nerve degeneration began in medulla
- Doesn't work if began in spinal cord
- ↑ lifespan or time before tracheostomy is required by 3-6 months

MOA

- Glutamate sodium channel antagonsit → reduce excessive activiation of neurons

Adverse Effects

- Well tolerated (partly because it does not do much…)
- Common: GI disturbances & somnolence
- Most serious: Hepatotoxicity

HUNTINGTON'S DISEASE (HD)

- Autosomal Dominant Adult-onset Disease
- No Cure ☹…Sx worsen with time until death
  - Progressive motor + cognitive decline

Clinical manifestation

↑↑ 'CAG' repeats within *Huntingtin* gene = Toxic Proteins → Basal Ganglia Degeneration = Enlarged Ventricles

- Onset of Sx inversely proportional to # of CAG repeats

Pathophysiology

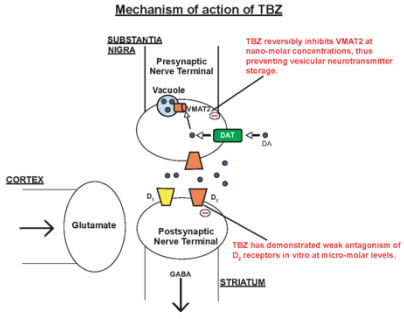
↓ **GABA neuron** → ↓ Substantia Nigra Inhibition = ↑ DA neuron activity → Hypotonia + Hyperkinesia

HD therapy

- Excessive DA activity = **Severe involountary & irregular movements (Chorea)**
  - Irregular movements
- ↓ DA release or block DA action
  - Different drugs to help manage BUT does not treat. Only increases QOL
- Drug-induced extrapyramidal symptoms can confound diagnosis of HD-related motor impairments!

Dopamine Blockers for Chorea of Huntington's Disease

Drug	Approved for HD	Major Side Effects
DRUGS THAT REDUCE DOPAMINE STORES		
Tetrabenazine [Xenazine, Nitoman ◆]	Yes	Depression, suicidal thoughts and actions
DRUGS THAT BLOCK DOPAMINE RECEPTORS		
First-Generation Antipsychotics		
Haloperidol [Haldol]	No	Extrapyramidal effects
Pimozide [Orap]	No	Extrapyramidal effects, sedation
Second-Generation Antipsychotics		
Risperidone [Risperdal]	No	Extrapyramidal effects, but less likely than with first-generation antipsychotics
Ziprasidone [Geodon]	No	
Quetiapine [Seroquel]	No	



HD Therapy: **Tetrabenazine**

- Clinical trials: 23.5% improvement of chorea's symptoms severity
- Benefits can last up to 5 years
- PO available / CYP2D6 hepatic metabolism

Major ADRs:

- Depression & Suicidal ideation
  - Mitigations: Behavior monitoring or antidepressant therapy
  - Depression may come from the disease progression itself (not the drug)

MOA

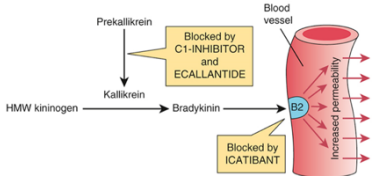
- Reversibly inhibits the VMAT at the vacules (VMAT pumps the dopamine inside the vesicle so that it can be release). By blocking, dopamine not going into the vesicles= not releasing.
- Also and antagonist at the D2 receptor (blocks the few dopamine that were released)

HEREDITARY ANGIOEDEMA (HAE)

- Rare hereditary deficiency in C1-esterase inhibitor (C1-INH) → Self-limited edema attacks
  - Angioedema (spontaenous & excessive edema in areas of the body) → from increased permeability of vessels
- Attacks last for 3-5 days and occur ≈ 10-14 days

S/SX

- Edema of larynx/facial area → Potentially fatal airway obstruction
- Intestinal edema → Severe cramping pain & vomiting



Drug therapy: **C1-estherase inhibitor**

MOA

- molecule that blocsk the conversion of pre kallikrein. = blocks formation of bradikinin= So you don't get the increased permeability.

HAE Drugs for Acute Management

C1 inhibitors

- Extracts from human C1-INH
- Only for abdominal or facial HAE
- May ↑ HAE pain
- Risk of hypersensitivity reactions

Ecallantide

- Efficient against all type of HAE
- Anaphylaxis in ≈ 4% of patients

Icatibant

- Efficient against all type of HAE
- Injection-site reactions in all patients

Androgens

- Only efficient for prophylaxis
- ↑ hepatic synthesis of C1-INH
- Significant hepatotoxicity

Tranexamic Acid

- Antifibrinolytic Rx (used for heavy menses)
- ↑ C1-Inhibitors concentrations
- Risks of thrombotic event
- Less efficient than other options