Ototoxic Medications

Ototoxicity is a common cause of hearing loss.

Over 200 medications, including aspirin, certain antibiotics and some anti-cancer drugs, are known to be ototoxic (which literally means "poisonous to the ears").

Incidence of Ototoxicity

- Furosemide 6-7%
- Aminoglycosides 63%
- Cisplatinin 23-50% in adults, 60% in children; some studies show elevated hearing thresholds in 100% of cisplatin patients in HFA (high frequency audiometry)

McKeage MJ. Comparative adverse effect profiles of platinum drugs. Drug Saf. 1995; 13:228-244.
Bisht M, Bist SS. Ototoxicity: the hidden menace. Indian J Otolaryngol Head Neck Surg. 2011:63:255-9.
Rybak LP. Ototoxicity of loop diuretics. Otolaryngol Clin North Am. 1993;26:829-44.

Ototoxic drugs

1. Salicylates and quinines (antimalarial) reversible

2. Loop diuretics - ethacrynic acid, furosemide, and bumetanide, torasemide, piratenide, azosemide, triflocin, indacrinone, indapamide reversible

3. Antibiotics - aminoglycosides & vancomycin irreversible; macrolides - erythromycin, azithromycin, clarithromycin reversible

4. Platinum-based chemotherapy - cisplatin and carboplatin irreversible

5. Phosphodiesterase-5 (PDE5) inhibitors - sildenafil, tadalafil, vardenafil, avanafil irreversible

Lanvers-Kaminsky C et al. Drug-Induced Ototoxicity: Mechanisms, Pharmacogenetics, and Protective Strategies. Clinical Pharmacology & Therapeutics, April 2017, 101(4), 491-500.

Ototoxic Drugs

- Drugs can affect cochlear function, vestibular function or both
- Symptoms: tinnitus, hyperacusis, aural fullness, hearing loss, dizziness, vertigo
- Temporary if stopped early enough - so early detection is important but - testing methods are variable in reliability
- Severity of HL is dose dependent and cumulative, other factors such as age, gender, comorbid conditions, genetic susceptibility, bioavailability and pre-existing hearing loss

Ganesan, Purushothaman et al. Ototoxicity: A Challenge in Diagnosis and Treatment. J Audiol tOol. 2018 Apr; 22(2): 59-68.

Ototoxic Medications

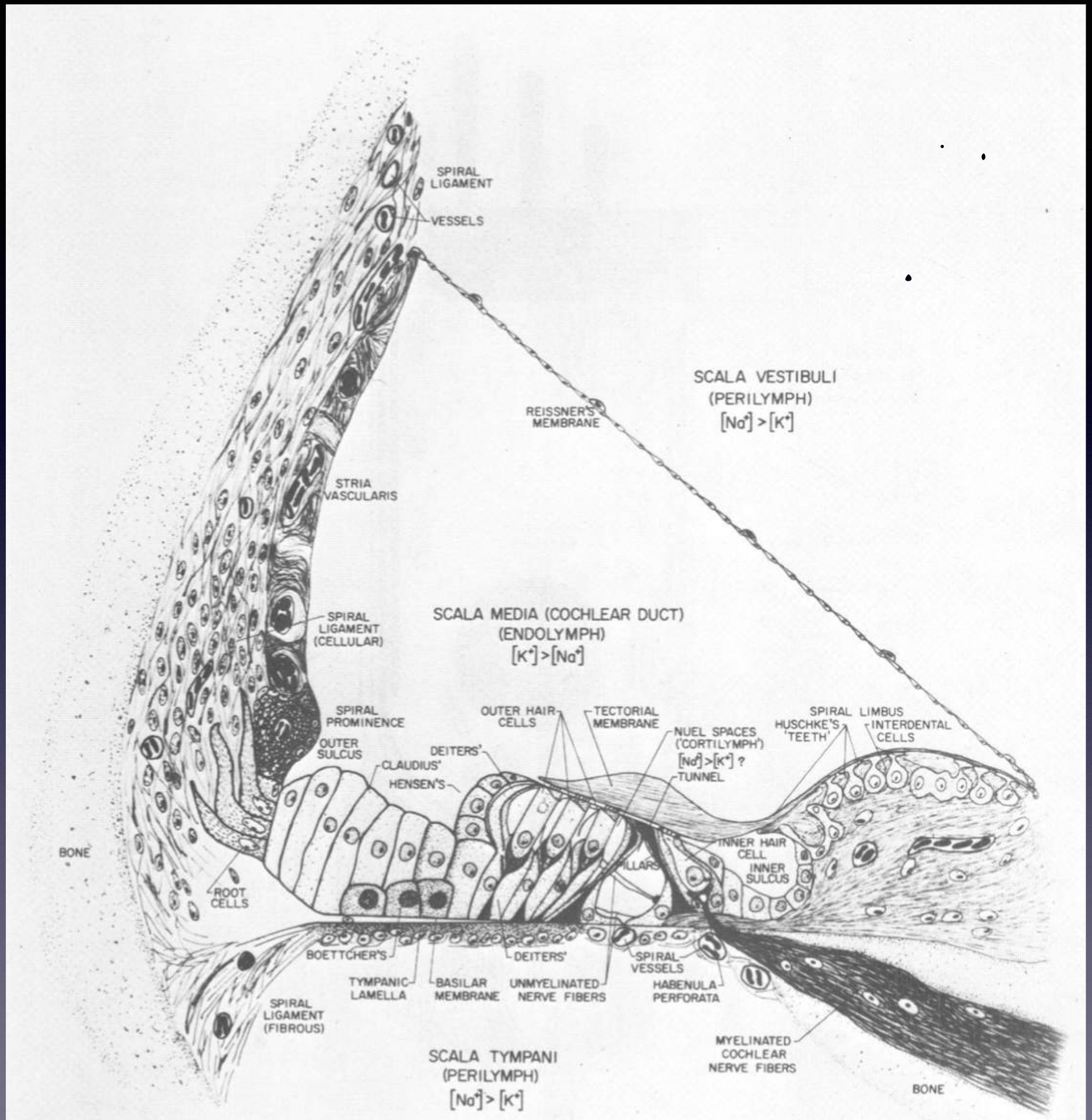
- Ototoxicity occurs primarily through damage of hair cells starting from highest frequencies first (above 8000Hz)
    - Extended high-frequency audiometry can be used to screen for ototoxicity
- Genetic susceptibility to ototoxic drugs can be attributed to mitochondrial DNA
    - So screen for family history of hearing loss

Koegel, Lawrence et al. Ototoxicity: A contemporary review of aminoglycosides, loop diuretics, acetylsalicylic acid, quinine, erythromycin, and cisplatinum. Am J Otology, March 1985, 6(2), 190-9.

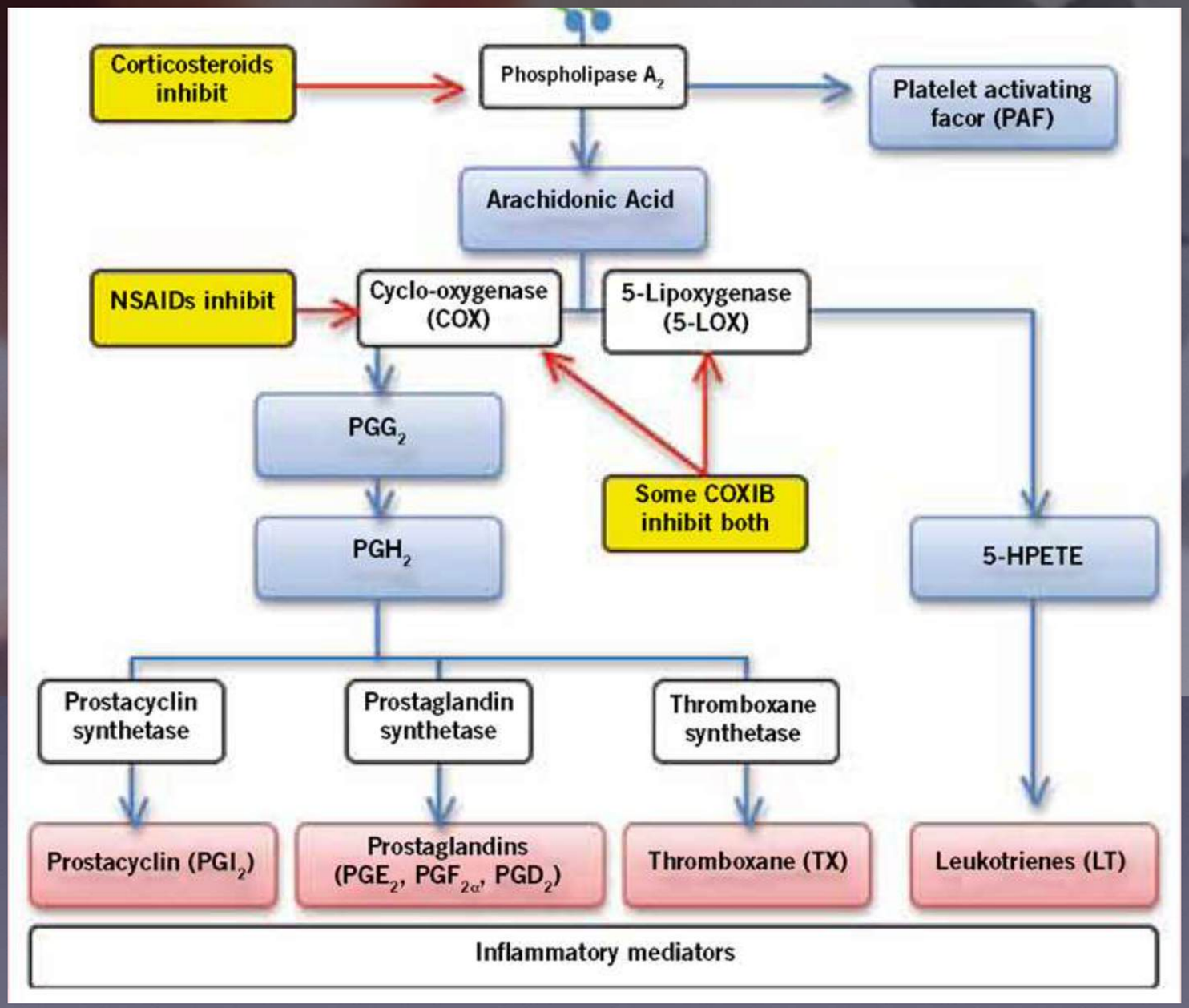
Mechanisms of Ototoxicity

- Salicylates and quinines promote vasoconstriction by reducing effects of prostaglandins causing reduced cochlear blood flow.
- Platinum chemo and aminoglycosides (AG) target outer hair cells at the basal turn by disrupting mitochondrial function via production of reactive oxygen species (ROS).
- Loop diuretics decrease blood flow via changes in circulating blood volume as well as interference with the stria vascularis.
- Macrolides and Phosphodiesterase-5 inhibitors are less understood.

Koegel, Lawrence et al. Ototoxicity: A contemporary review of aminoglycosides, loop diuretics, acetylsalicylic acid, quinine, erythromycin, and cisplatinum. Am J Otology, March 1985, 6(2), 190-9.
Rizk Habib et al. Drug-Induced Ototoxicity: A Comprehensive Review and Reference Guide. Pharmacotherapy, 2020, 40(12), 1265-75.


SPIRAL LIGAMENT
VESSELS
REISSNER'S MEMBRANE
SCALA VESTIBULI
(PERILYMPH)
[Na+] > [K+]
STRIA VASCULARIS
SPIRAL LIGAMENT (CELLULAR)
SCALA MEDIA (COCHLEAR DUCT)
(ENDOLYMPH)
[K+] > [Na+]
SPIRAL PROMINENCE
OUTER SULCUS
CLAUDIUS'
HENSEN'S
DEITERS'
OUTER HAIR CELLS
TECTORIAL MEMBRANE
NUEL SPACES ('CORTILYMPH')
[Na+] > [K+] ?
TUNNEL
SPIRAL LIMBUS
HUSCHKE'S 'TEETH'
INTERDENTAL CELLS
INNER HAIR CELL
INNER SULCUS
BONE
ROOT CELLS
BOETTCHER'S
DEITERS'
SPIRAL VESSELS
TYMPANIC LAMELLA
BASILAR MEMBRANE
UNMYELINATED NERVE FIBERS
HABENULA PERFORATA
SPIRAL LIGAMENT (FIBROUS)
MYELINATED COCHLEAR NERVE FIBERS
SCALA TYMPANI
(PERILYMPH)
[Na+] > [K+]
BONE

Salicylates and NSAIDs



Salicylates and NSAIDs

- Aspirin ototoxicity occurs 11 per 1000 patients
- Reversible cochlear hearing loss of all frequencies bilaterally which rarely becomes permanent, usually recovers within 24-72 hours after stopping aspirin
- Vasoconstriction in the stria vascularis and blockage of the spiral vessels in the basilar membrane reducing blood supply to the organ of Corti by inhibiting cyclo-oxygenase and reducing prostaglandins

Boettcher, Flint et al. Salicylate Ototoxicity: Review and Synthesis. Am J Otolaryngol; 12:33-47, 1991.
Jung, Timothy T.K. et al. Ototoxicity of Salicylate, Nonsteroidal Anti-Inflammatory Drugs, and Quinine. Otolaryngologic Clinics of North America, October, 1993, 26(5), 791-810.

Salicylates and NSAIDs

- Salicylism: N/V, tinnitus, HL, HA, confusion, increased pulse and respiration
- Elderly are at higher risk even at lower doses
- Ototoxicity has been observed following topical application of salicylates to the skin for psoriasis
- Aspirin ototoxicity is dose-dependent
- Salicylate hearing loss was completely prevented by subQ injection of zinc 6mg/kg

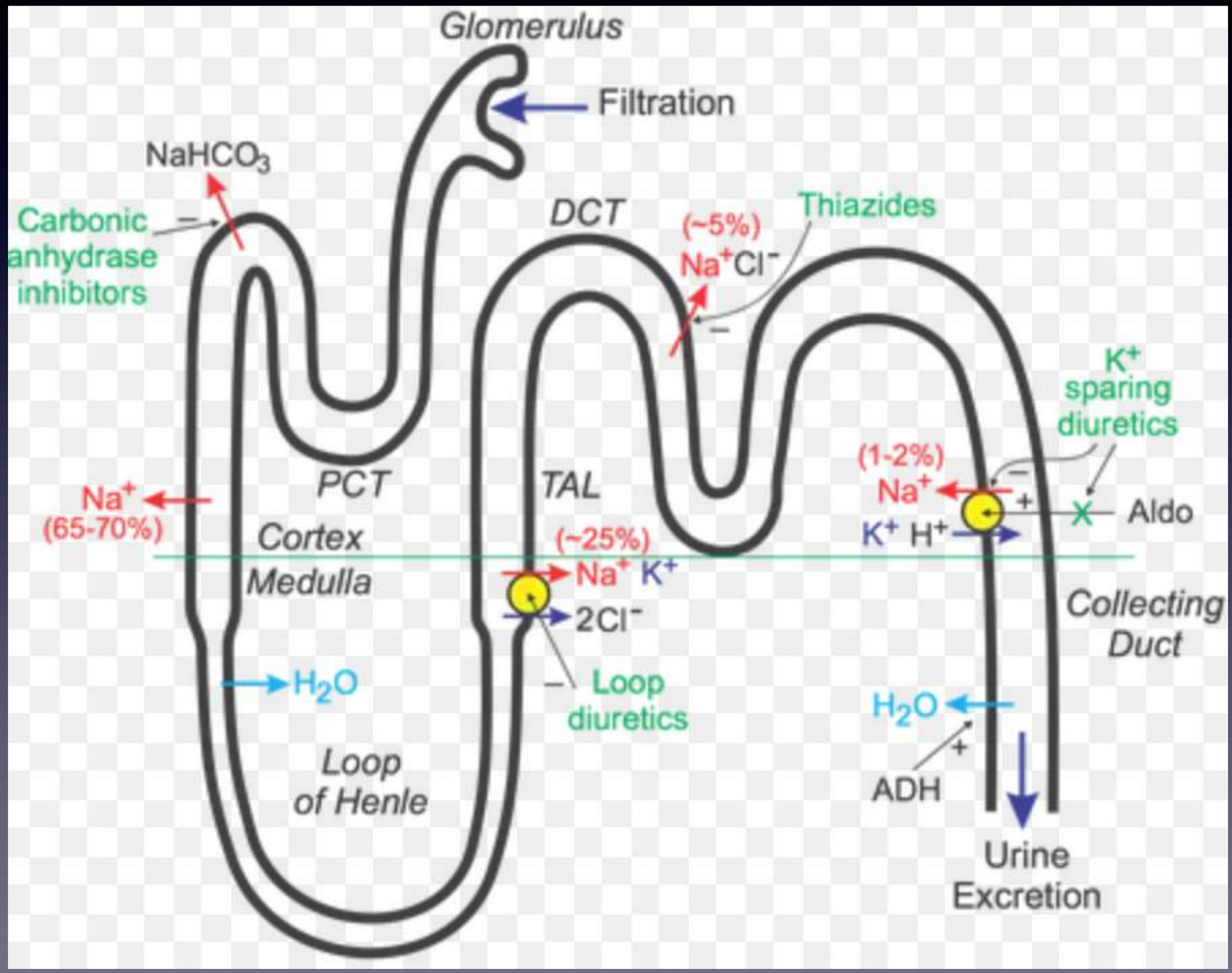
Jung, Timothy et al. Ototoxicity of salicylate, non steroidal anti-inflammatory drugs, and qunine. Otolaryngologic Clinics of North America, 26(5), October 1993, 791-810

Gunther T et al. Protection against salicylate ototoxicity by zinc. J Trace Elem Electrolytes Health Dis. 3(1), Mar 1989, 51-3.

Quinine

- Quinine (from bark of the cinchona tree) is used for leg cramping, chloroquine and hydroxychloroquine for malaria and autoimmune diseases and Covid-19. Quinidine (isomer) is used for arrhythmias. Quinine is also used in tonic water.
    - Increased resistance of plasmodium falciparum to chloroquine has caused increased use of quinine for malaria treatment.
- Plasma levels fall rapidly upon termination of therapy within 24 hours so hearing loss is usually reversible and dose-dependent.
- Cinchonism (with high dose use): transient tinnitus, hearing loss, vertigo, headache, nausea, and vision changes.

Loop Diuretics



Loop Diuretics

- Loop diuretics: furosemide, bumetanide, and ethacrynic acid, also piretamide, azosemide, triflocin, and indapamide
- Exact mechanism is unknown:
    - Inhibits Na-K-Cl transporter thus disturbing the ionic concentration of the endolymph (endocochlear potential) which is dose-related and reversible
    - Stria vascularis (decreased blood flow) is the major site of loop diuretic ototoxicity
        - Inhibition of adenylate cyclase
- Affects basal turn of cochlea as well as cristae and macula - (outer hair cell loss)
- Symptoms include hearing loss, tinnitus and vertigo - 90% are reversible recovering within 24 hours but can become permanent
    - Furosemide ototoxicity is usually rapid onset and quickly reversible, while ethacrynic acid has a more gradual onset with longer recovery.

Rybak, Leonard P. Ototoxicity of loop diuretic. Otolaryngologic Clinics of North America, 26(5), October 1993, 829-843.
Rybak, Leonard P. Pathophysiology of furosemide ototoxicity. The Journal of Otolaryngology 11:2, 127-133.

Loop Diuretics

Risk factors for ototoxicity

- Rapid IV infusion increases the incidence of ototoxicity. Hearing loss can occur after acute IV injection or after longterm oral therapy - so should be given via slow IV continuous infusion or divided oral doses
    - infused at a rate less than 5.6 mg/min did not cause ototoxicity while 25 mg/min did cause ototoxicity
- Renal, liver, and cardiac disease
- Patients receiving aminoglycoside antibiotics or cisplatin along with loop diuretic (There was no synergistic effect with noise and loop diuretic)
- Premature infants are at increased risk - avoid more than 2mg/kg per day.
- ✤If loop diuretic patient has ototoxic symptoms: order audiogram and change the diuretic - changing from furosemide to bumetanide seemed to allow for recovery

Rybak, Leonard P. Pathophysiology of furosemide ototoxicity. The Journal of Otolaryngology, 11(2), April 1982, 127-133.

Aminoglycosides

Aminoglycosides

(Two categories)

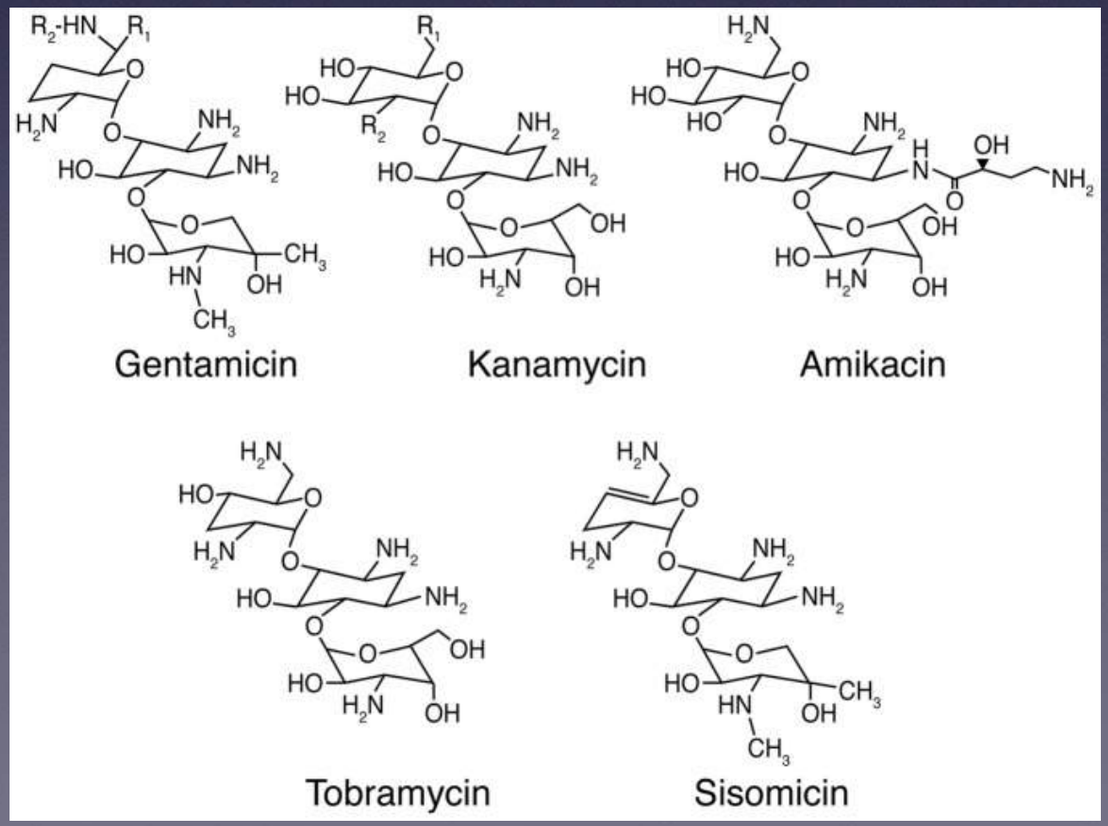
Isolated from *Streptomyces*	Isolated from *Micromonospora*
Neomycin	Gentamycin
Kanamycin	Sisomicin
Tobramycin	Netilmicin
Amikacin	
Streptomycin	

- Common uses include resistant TB, sepsis, respiratory infections *Pseudomonas aeruginosa* in CF, complex UTIs, endocarditis.
- Low cost and still high infection rates of TB make AG widely used around the world.

Aminoglycosides

Cochleototoxic (Free amino -NH^2 groups)	Vestibulotoxic (Free methyl amine -$NHCH^3$ groups
Amikacin	Gentamycin
Neomycin	Streptomycin
Kanamycin	

Tobramycin



Aminoglycosides

- affects high frequencies first (destruction of outer hair cells in the basal cochlea occurs before inner hair cells at the apex)

- especially in renal impairment, elderly,

- potentiates effects of other ototoxic drugs

- 10-15% cochlear toxicity; 5-15% vestibular toxicity (for gent and tobra)

Matz, Gregory J. Aminoglycoside Ototoxicity. Am J Otolaryngol. March 1986, 7(2), p117-119.
Smith CR et al. Double blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. N Engl J Med, 1980, 1106-1108.

Aminoglycosides

- AG concentration in perilymph peaks 2-5 hours after injection at 3-5% of peak serum level
- Serum half life is 80 minutes but half-life in perilymph is 5-15 hours after a single dose. After multiple doses, the elimination half-life increased up to 30 days.
- So rapid accumulation in the perilymph causes hair cell death ->inhibits protein synthesis affecting cellular repair
- AG enter cochlear cells via mechanoelectrical transducer (MET) channel in outer hair cells which act as one-way valves, trapping the AG inside the cells.
- Vestibular ototoxicity also occurs by damage of hair cells in the cristae

Jiang, Meiyan. Aminoglydoside-Induced Cochleotoxicity: A Review. Front Cell Neurosci 2017; 11:308, p 1-31.

Aminoglycoside Vestibulotoxicity

- Gentamicin is particularly toxic to type 1 vestibular hair cells
- Because both ears are affected simultaneously, symptoms can include ataxia and oscillopsia without nystagmus, vertigo, or hearing loss
- Vestibulotoxicity can occur with normal renal function and even with keeping peak and trough levels within normal limits (false sense of security) - frequent cause of malpractice cases
    - Single daily dosing more risky than multiple daily dosing
    - Prolonged duration of treatment > 14 days
- Delayed onset after cessation of treatment can occur 1-10 days later (4 days average)
- Affects angular acceleration (SCC) more than linear (saccule/utricle)

Rutka, John. Aminoglycoside Vestibulotoxicity. Lea J, Pothier D (eds): Vestibular Disorders. Adv Otorhinoolaryngol Basel, Karger, 2019, vol 82, pp101-110

Aminoglycosides

- Doubling dose of kanamycin doubles the plasma concentration (linear relation) but increases perilymph concentration 10x so small increases in dose magnify the ototoxic effects

- Longer perilymph excretion time such as neomycin (55 hours) has highest ototoxicity while short perilymph excretion time such as streptomycin (24 hours) is the least ototoxic

- Neomycin can cause hearing loss when given

  - Intratympanic ear drops theoretically - although a study of 446 children getting BM&T showed no SNHL after 2 weeks of polymyxin B-neomycin-dexamethasone ear drops

  - High doses oral (used for hepatic encephalopathy), colonic irrigation, (poor G.I. absorption in low dose)

  - Intrapleural installation

- Crosses placenta and causes fetal hearing loss so should be avoided in pregnancy

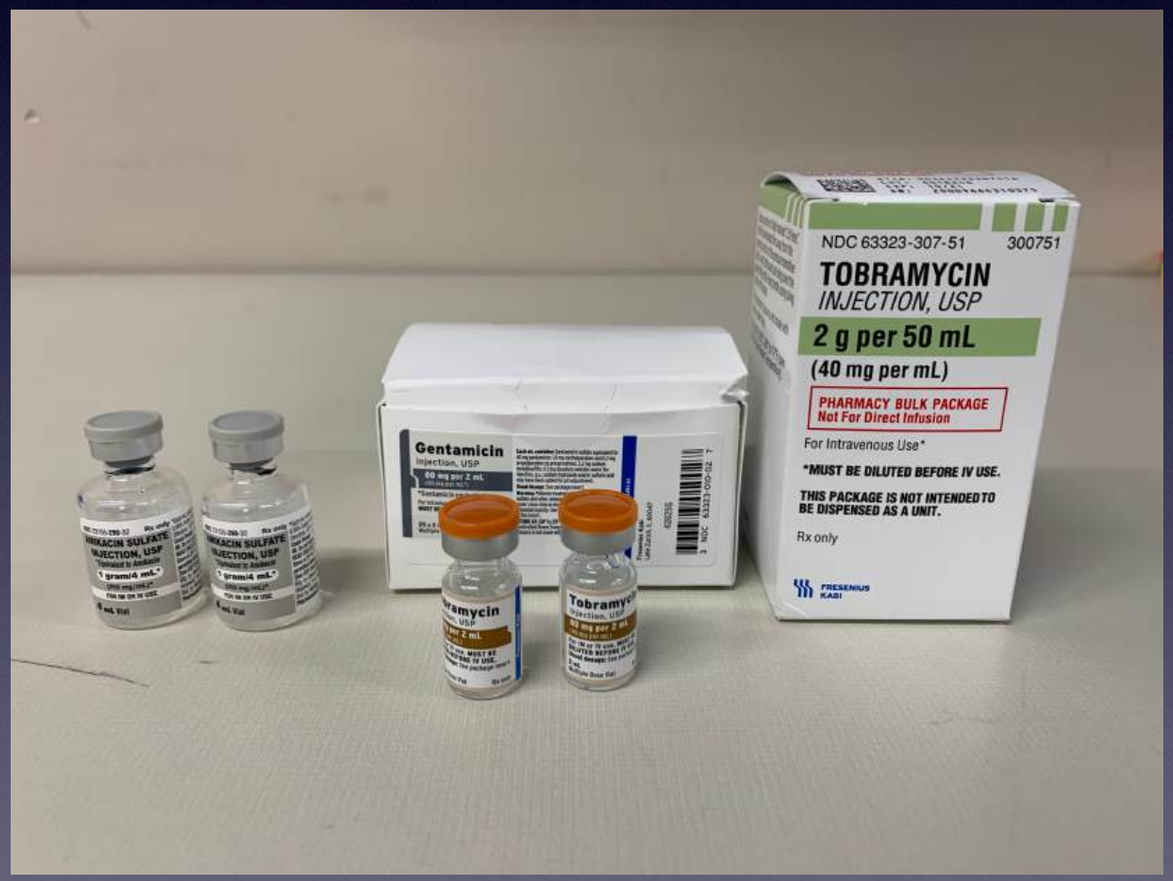
Rakover,Y et al. Safety of topical ear drops containing ototoxic antibiotics. J Otolaryngol. 1997, Jun;26(3): 194-6.

Aminoglycoside Ototoxicity

- Cochlear toxicity: 16.4% gentamicin, 15.3% tobramycin
- Vestibular toxicity: 15.1% gentamicin, 4.5% tobramycin
- Both drugs cause ototoxicity after discontinuation of treatment
- AG ototoxicity could be unilateral, delayed onset (mean 11 days after onset of treatment) and reversible (55% improve but could take as long as 9 months)
- Most patients who were found to have drop in PTA or ENG were asymptomatic (only 5% were symptomatic)

Risk Factors for Aminoglycoside Ototoxicity

1. Duration of therapy greater than 10 days
2. Elevated serum levels
3. Frequent doses
4. Renal dysfunction
5. Higher age
6. Noise exposure
7. Pre-existing hearing loss
8. Coadministration with other ototoxic or nephrotoxic drugs



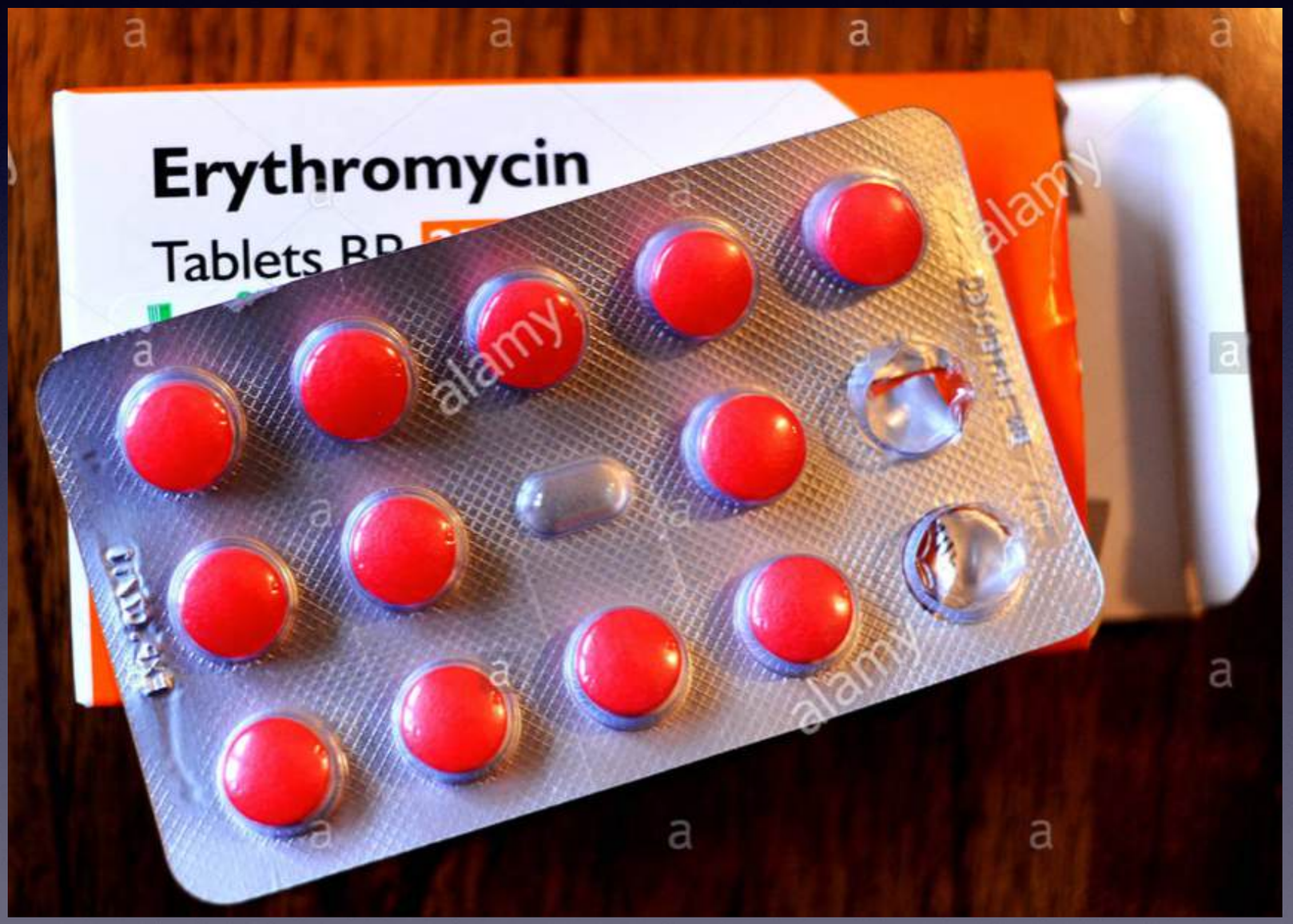
Pharmacogenetics of amino glycoside ototoxicity

- Maternally inherited trait caused by mutations in mitochondrial 12SrRNA (A1555G and C1494T mutations) -> increased risk for aminoglycoside cochleototoxicity.
    - 10-33% of Asians and 17% of whites who had AG ototoxicity carried this mutation while the overall prevalence of the mutation in white patients is 0.2%
    - Most prevalent in Chinese.
    - Patients with this mutation also are at higher risk for presbycusis.

Nguyen, Tiền et al. Genetic susceptibility to aminoglycoside ototoxicity. International Journal of Pediatric Otorhinolaryngology. 120(2019), p15-19.

Macrolide Ototoxicity

Erythromycin, Clarithromycin, and Azithromycin

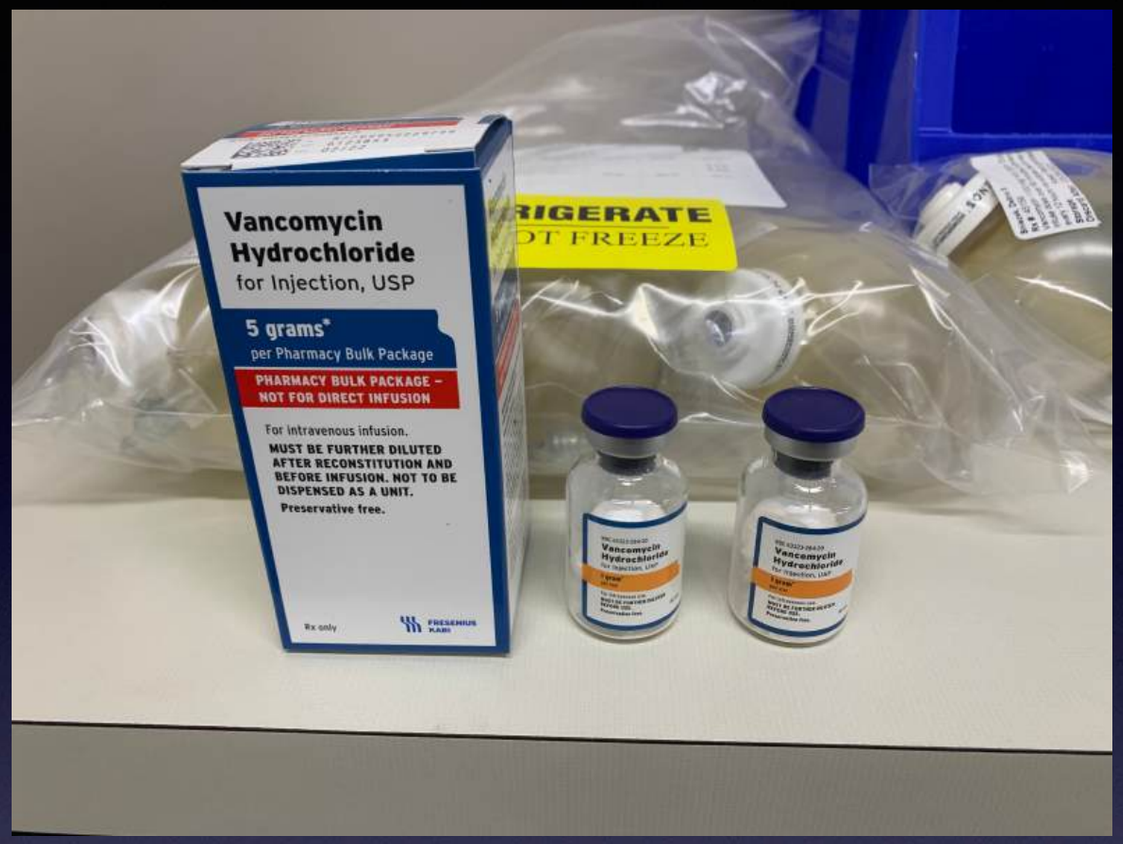


Macrolide Ototoxicity

- Used for treatment of chlamydia and syphilis.
- Tinnitus and bilateral symmetric SNHL of 40-50 dB within 2-7 days after starting, and resolves 1-3 weeks after cessation. Occasional permanent hearing loss has been reported.
- Ototoxicity is likely due to transient dysfunction of the stria vascularis due to inhibition of ion transport.
- Ototoxicity occurs usually with large doses (more than 4 gm per day).

Swanson, DJ et al. Erythromycin ototoxicity: prospective assessment with serum concentrations and audiograms in a study of patients with pneumonia. Am J Med. 1992 Jan; 92(1): 61-68.

Vancomycin Ototoxicity

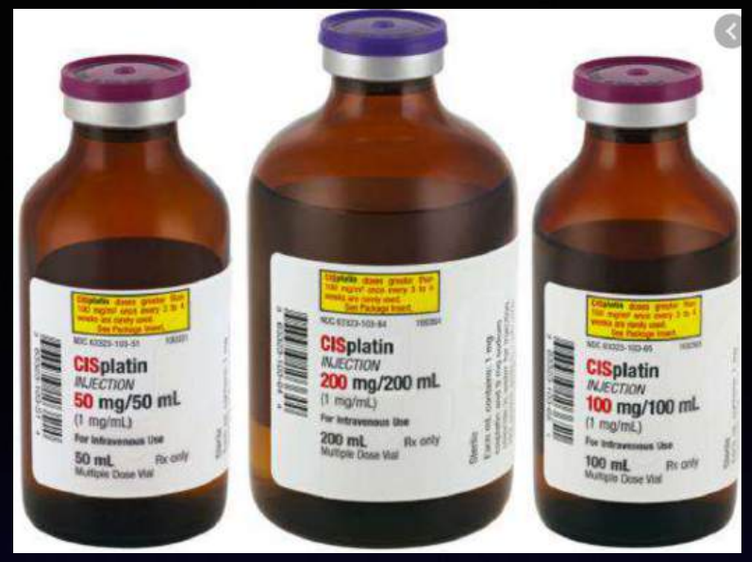


- Vancomycin is a glycopeptide antibiotic used for MRSA, strep endocarditis, and Clostridium difficile enterocolitis

- Low risk (8%) of irreversible high-frequency SNHL in older patients (serum levels > 30mcg/ml)

Humphrey, Clayton et al. Long-term vancomycin use had low risk of ototoxicity. Published online 2019 Nov.6, PLoS One 14(11), p1-26. PMID: 31693679

Platinum-based chemotherapy



- Cisplatin, carboplatin and oxaliplatin are the only FDA-approved platinum compounds. Carboplatin and oxaliplatin are less ototoxic than cisplatin.

- Side effects: ototoxicity, nephrotoxicity, neurotoxicity, GI toxicity, and myelosuppression

- Affects outer hair cells of basal turn and spiral ganglion and degeneration of stria vascularis

Baguley, David M et al, Looking beyond the audiogram in ototoxicity associated with platinum-based chemotherapy. Cancer Chemother Pharmacy. 2020; 85(2): 245-250.

Platinum-based chemotherapy

- Irreversible, dose-related SNHL in 4-8 kHz occurs in 11% of patients, tinnitus can persist for at least a year in 38% of cases.
- Hearing loss usually starts days to weeks after treatment and is mostly bilateral, can even worsen after end of treatment so recommend audio 1 and 3 months after treatment.
- Higher risk patients include: children, renal insufficiency, pre-existing hearing loss.
- Avoid coadministration of other ototoxic drugs such as aminoglycosides or loop diuretics

Landier, Wendy. Ototoxicity and cancer therapy. Cancer. 09Feb2016, 1-35.

Platinum-based chemotherapy

- Aggressive hydration helps reduce side effects
- Incidence and degree of hearing loss increased with increasing individual and cumulative doses
- Fast bolus infusion caused significantly more hearing loss than slow infusion over 2 hours (but no benefit between slow infusions and continuous infusions.)
- High-frequency audiometry (10-16 kHz) should be performed before starting therapy and before each successive dose.
- Vestibulotoxic: vertigo, imbalance and oscillopsia (underreported)

Platinum Ototoxicity in Children

- Greatly improved survival in pediatric oncology: germ cell tumors, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, Wilms tumor, refractory lymphoma

- Ototoxicity: cisplatin > carboplatin > oxaliplatin
    - Cumulative dose cisplatin/carboplatin > 400mg/m^2 in children and >600mg/m^2 in adults

- Children < 5 years old = highest risk

- Administer without noise and avoid bolus infusion

- Genetic predisposition seems to play a role

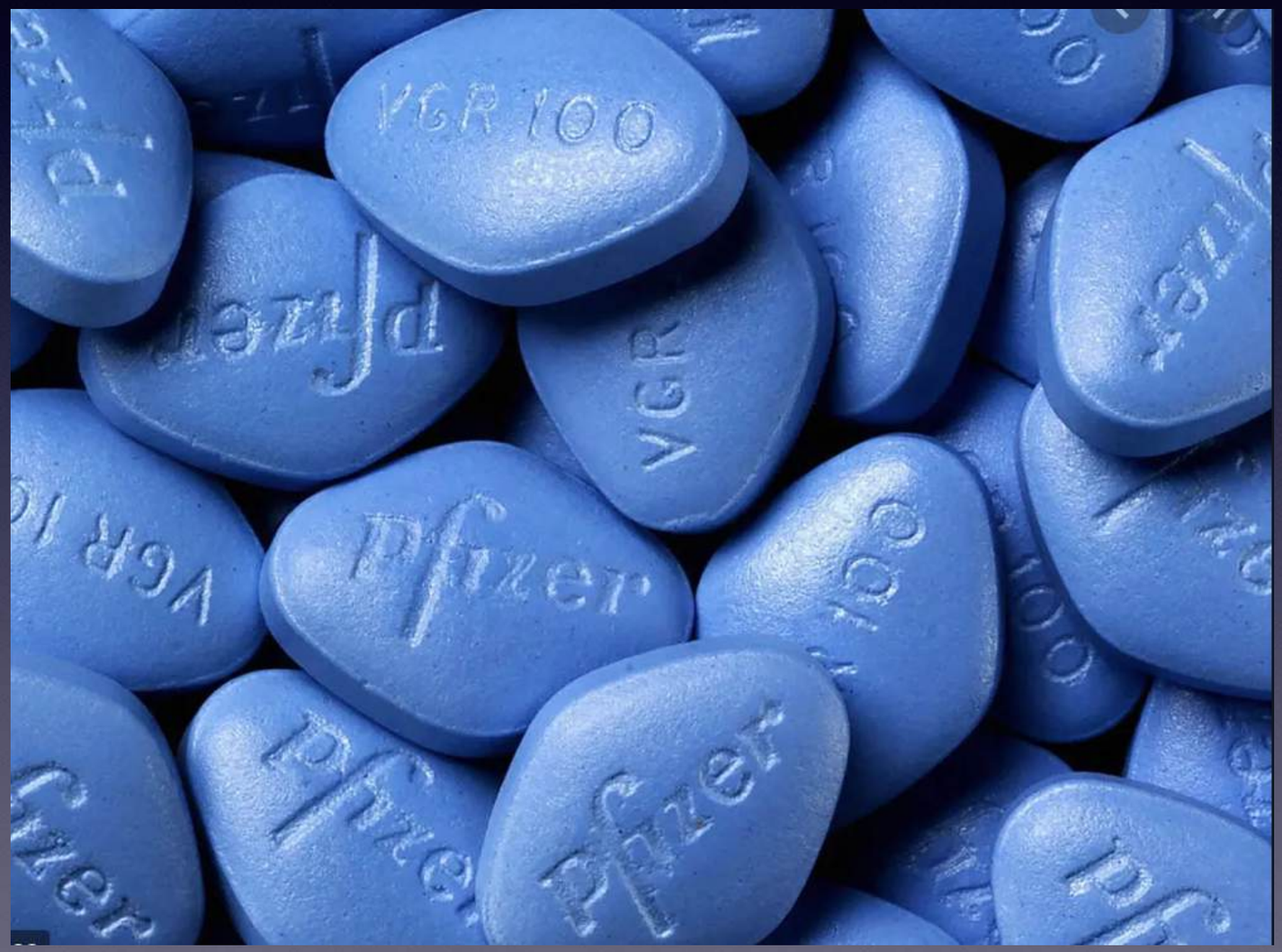
Romano, Alberto et al. Assessment and Management of Platinum-Related Ototoxicity in Children Treated for Cancer. Cancers 2020 May; 12(5) 1266. Published online PMID: 32429551

Platinum Ototoxicity in Children

- Hearing loss incidence: cisplatin 25%, carboplatin 19%, treated with both 35%, further progression after end of chemo 8.6%.
- Audiometry should be done at baseline, and 24 hours prior to each course of chemo, and any clinical sign of hearing loss, and at the end of treatment.
- Hearing loss can manifest many years later so audio:
  - Annually for kids < 6yrs, every 2 years ages 6-12, and every 5 years for older than 12 years.
- Many evaluation scales for hearing loss due to chemotherapy: Brock criteria, National Cancer Institute, American Speech-Language Hearing Association, New International Society of Pediatric Oncology (SIOP).

Romano, Alberto et al. Assessment and Management of Platinum-Related Ototoxicity in Children Treated for Cancer. Cancers 2020 May; 12(5) 1266. Published online PMID: 32429551

Phosphodiesterase-5 Inhibitors (PDE-5)



Phosphodiesterase-5 Inhibitors (PDE-5)

- Inhibits the enzyme PDE-5 that degrades cGMP which leads to smooth muscle relaxation and therefore vasodilation
- SNHL may be associated with tinnitus (22%), dizziness (33%)
- Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra)
- Phosphodiesterase enzymes are found in rod and cone photoreceptor cells of the retina (vision loss)
- Also used to treat pulmonary hypertension
- ★ All prospective studies have failed to find an association regarding PDE-5 inhibitor use and ototoxicity but a link seems likely by case reports and retrospective data.
- Since 2007, FDA mandates warning label of potential risk of sudden SNHL.

Manna Sayan et al. Phosphodiesterase-5 (PDE-5) Inhibitors and Ototoxicity: A Systematic Review. Otology & Neurotology. 2019; 40: 276-283.

Phosphodiesterase-5 Inhibitors (PDE-5)

- Majority of hearing loss is unilateral 75%, 25% were bilateral.
- Usually occurs within 24 hours of taking the drug (67-88%)
- Can be reversible (32%) or permanent
- Siladenafil > 50% of cases

Khan, Afroze Shah et al. Viagra Deafness—Sensorineural Hearing Loss and Phosphodiesterase-5 Inhibitors. The Laryngoscope. May 2011; 121, 1049-1054.

Leslie Seith, et al. Siladenafil and Furosemide Associated Ototoxicity: Consideration of Drug-Drug Interactions, Synergy, and Broader Clinical Relevance. J Popul There Clin Pharmacol Vol 20(2):e128-e131; June 12, 2013.

Ototoxicity of Noise and Drugs in Combination

- Guinea pig cochlea studies: Low dose ototoxic drugs and limited noise exposure combined can cause hearing loss that does not occur if applied separately

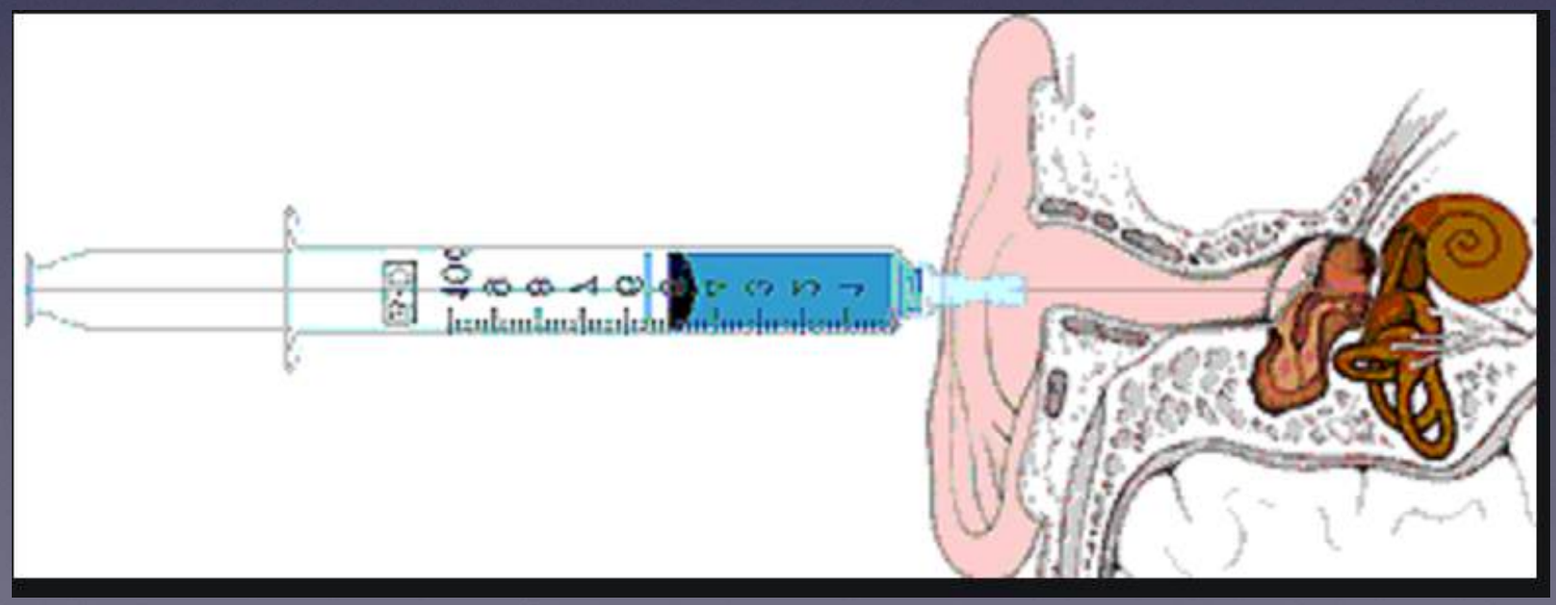
- Ototoxic drugs produces increased susceptibility to noise damage and vice versa

Dayal,V.S.,Kokshanian,A.andMitchell,D.P. 1971. Combined Effects of Noise and Kanamycin. Ann. Otol. 80: 897.

Quante, M., Stupp, H. and Brun, J. P. 1970. Ototoxikosen unter Larmbelastung, Archiv fur Klinische und Experimentelle Ohren-, Nasen-, und Kehikopfheilkunde 196: 233.

Intratympanic Aminoglycosides

- Ablative treatment for Meniere's disease
  - Streptomycin replaced by gentamicin
- More vestibulotoxic than cochleotoxic



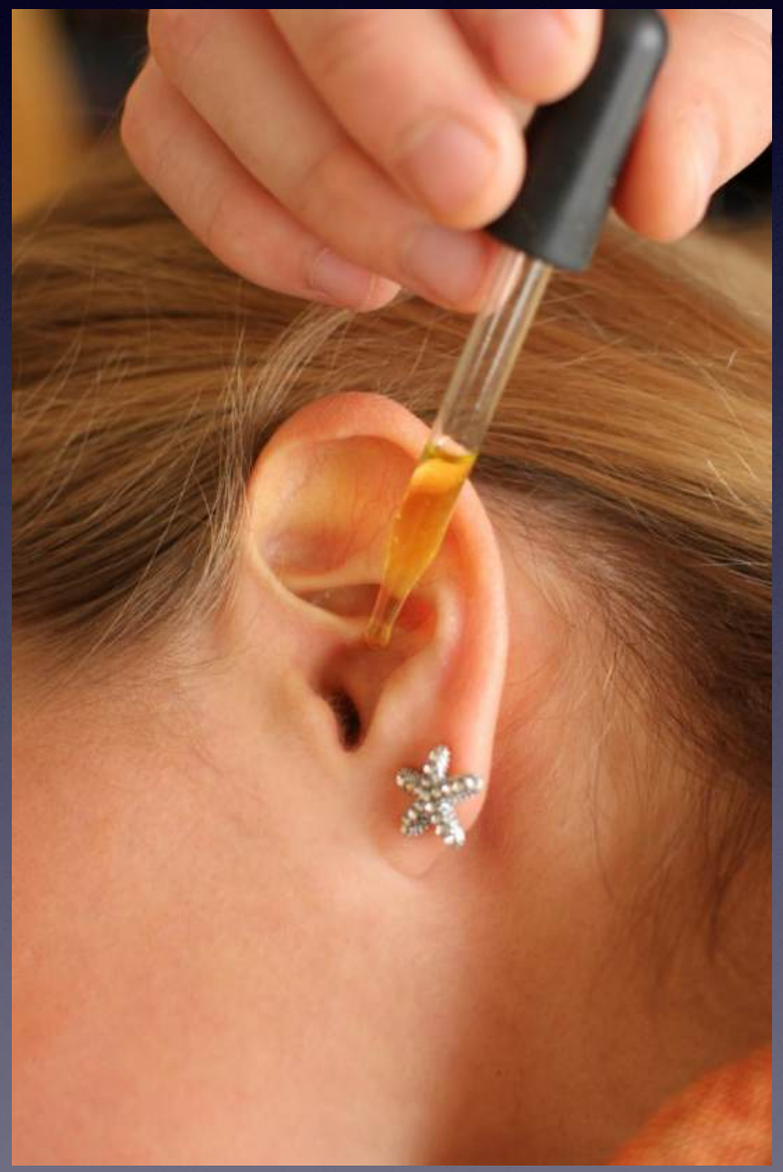
Toxicity of Ototopical Medications

1.Antibiotic drops

- Neomycin (cortisporin)
- Quinolones

2.Antifungal drops

- Ketoconazole
- Itraconazole
- Nystatin
- Gentian violet
- Natamycin



3.Antiseptics

- Acetic acid
- Boric acid
- Alcohol
- Povidone-iodine
- Chlorhexidine

Toxicity of Ototopical Neomycin

Cortisporin (polymyxin, neomycin, hydrocortisone) drops

- Risk increases with prolonged use
- Risk is higher in a healthy, non draining ear
- 2014 AAO clinical practice guideline advises against use in a non intact TM

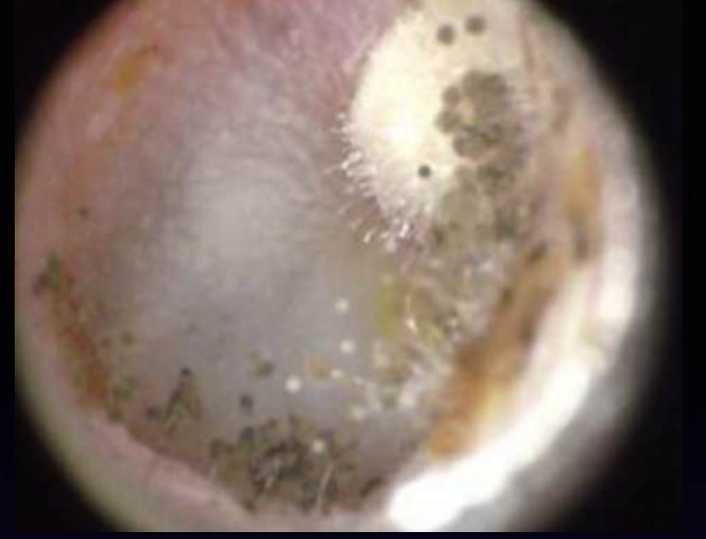
Rizk HB. Drug-induced ototoxicity: a comprehensive review and reference guide. Pharmacotherapy 40(12) 2020, 1265-75.
Rakover, Y et al. Safety of topical ear drops containing ototoxic antibiotics. J Otolaryngol. 1997 Jun; 26(3), 194-6.

Topical Quinolones Ofloxacin and Ciprofloxacin

- The only US FDA approved topical antimicrobial for use in a non-intact TM
- No evidence of ototoxicity in all animal models and clinical trials
- Steroids may increase the risk of TM perf in animal models

Dirain CO et al. Commercial quinolone ear drops cause perforations in intact rat tympanic membranes. Otol Neurotol 2019;10:1386-91.

Antifungal Drops



- No toxicity with intact TMs.
- Antifungals are not water soluble so must be mixed with alcohol-based solvents for liquid form and alcohol is ototoxic
- Ketoconazole and itraconazole - cause tinnitus and hearing loss is less than 2% of cases
- Nystatin - no ototoxicity in clinical use (animal data controversial)
- Gentian violet (aniline dye) -
    - Anti-inflammatory, antifungal, antibacterial
    - Seems to cause extensive cochlear and vestibular damage in animal models
- Natamycin (Natacyn) ophthalmic suspension is a topical anti fungal - seems safe with TM perforation

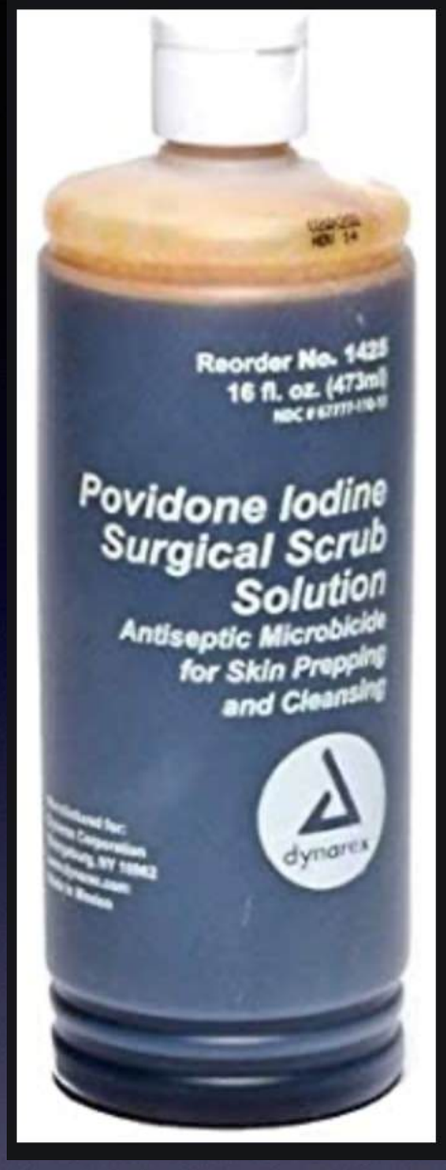
Tom LW. Ototoxicity of common topical antimycotic preparations. Laryngoscope 2000;4:509-16.

Topical Antiseptics

Acetic acid and alcohol topically ototoxic

- Iodine and non-alcohol-based and non detergent solutions are the safest preps prior to ear surgery

- Evidence was weak evidence of ototoxicity but iodine seems to cause the least harm while chlorhexidine and high concentration of alcohol based solutions showed most harm



- No clear evidence for or against ototoxicity regarding: boric acid, acetic acid, aluminum acetate, povidone iodine

Singh Shubhi et al. Systematic review of ototoxic pre-surgical antiseptic preparations — what is the evidence? J Otolaryngol Head Neck Surg. 2018; 47: 18.

Monitoring of Ototoxicity

- Monitoring can detect subclinical ototoxicity allowing early intervention such as
  - Treatment alternatives
  - Dose modifications
  - Application of otoprotective substances

Monitoring of Ototoxicity

- Conventional PTA: air conduction 250-8000 Hz and bone conduction 250-6000 Hz
- HFA High frequency audiometry (8-20 kHz)
- DPOAE 1-8 kHz - specificity rate of 78%
    - Pros: frequency specific, able to measure over broader frequency ranges, quickly done at bedside
    - Cons: sensitive to middle ear dysfunction, not detectable in thresholds > 60 dB
- Ototoxicity hearing shifts occurred first in HFA, then DPOAE and last in conventional PTA
- ABR restricted to 500-4000 Hz but can use bird chirp recordings up to 6000 Hz
- SRO_{BEH} - (sensitive range of ototoxicity using PTA and HFA) unique for each patient's audiometry defined as the highest frequency with a threshold < 100 dB followed by 6 lower consecutive frequencies in 1/6th octave steps.
    - Reduces test time while maintaining sensitivity (90%)
- Self-evaluating questionnaires: THI Tinnitus Handicapped Inventory & DHI Dizziness Handicapped Inventory
- Vestibular monitoring: dynamic visual acuity and head impulse test
    - Use both SRO_{BEH} and DPOAE
- Monitoring is expensive, time-consuming, and difficult in chronically ill patients.

- Konrad-Martin D. Proposed comprehensive ototoxicity monitoring program for VA healthcare (COMP-VA). J Rehabil Res Dev. 2014; 51:81-100.

Treatment of Ototoxicity

- No FDA approved treatments for ototoxicity

- Antioxidants - coenzyme Q10, D- & L-methionine, thiourea, vitamins B, C, & E, N-acetylcysteine.

- Intratympanic injection of N-acetylcysteine and IT dexamethasone IT PRP (platelet-rich plasma) and vitamin E showed positive results in preventing cisplatin-induced ototoxicity.

- Hyperbaric oxygen, vitamin C, triamterene, and propranolol helps prevents ototoxicity of loop diuretics (in animal models)

- Rapamycin - antifungal metabolite produced by Streptomyces hygroscopicus used as an immunosuppressant drug to prevent kidney transplant rejection - has otoprotective effects.

- Amifostine and sodium thiosulfate: free radical scavengers otoprotective but may protect tumor cells from platinum drugs

Riga MG et al. Transtympanic injections of N-acetylcysteine for the prevention of cisplatin-induced ototoxicity: a feasible method with promising efficacy. Am J Clin Oncol. 2013; 36:1-6.
Marshak T et al. Prevention of cisplatin-induced hearing loss by intratympanic dexamethasone: a Randomized Controlled Study. Otolaryngol Head Neck Surg. 2014; 150:983-90.
Yurtsever, Kum Nurcan, et al The Protective Effect of Platelet Rich Plasma Against Cisplatin-Induced Ototoxicity. J Craniofac Surg. July-Aug 2020; 31(5).

Oricula Therapeutics

Medicines to Preserve Hearing

Preserving hearing is our mission

ORC-13661

- Oral drug currently in FDA-approved human clinical trials - highly protective for hearing and balance against ototoxic medications including aminoglycosides and cisplatin as well as aging

- Research collaboration between University of Washington and the Fred Hutchinson Cancer Research Center licensed to Oricula Therapeutics (Seattle) and Decibel Therapeutics (Boston)

- U.S. patents valid through 2036 and global filings are in process

- ORC-13661, an oral medication to preserve hearing during AG therapy has completed Phase 1 clinical testing in normal human volunteers for safety, tolerability, and pharmacokinetics. Well tolerated at doses 3x above the clinical dose.

- Phase 2 proof of efficacy clinical trial in non-TB mycobactium (NTM) patients with severe lung infections is planned. Over 35% of NTM patients treated with IV amikacin for up to 90 Days develop significant hearing loss. Our preliminary calculations, suggest that we can power the demonstration of human efficacy of ORC-13661 with less than twenty patients per treatment group.

ORC-13661

- Reversibly blocks the hair cell MET channel (mechanoelectrical transducer) - may provide protection at multiple levels
- Dose dependent otoprotectant across multiple species and toxins
    - Protects against hair cell survival and hearing loss with increasing doses against gentamicin, amikacin, neomycin, & cisplatin
    - Tested in mice cochlear cultures, rats with ABR, zebrafish,
- ORC-13661 therapeutic dose = 5mg/kg. Does cause hearing loss at 200mg/kg dose
- Well tolerated and no interference with antimicrobial efficacy of AGs

Kitcher, Sian R et al. ORC-13661 protects sensory hair cells from amino glycoside and cisplatin ototoxicity. JCI Insight. 2019; 4(15), p1-19.

Top 10 Take Home Points

10. Reversible: ASA, quinines, loop, macrolides.
Irreversible: aminoglycosides, vanco, platinum, PDE5?

9. Early detection with HFA because basal turn (high frequency) affected first

8. Consider family h/o ototoxicity (gene susceptibility)

7. Avoid multiple insults - other ototoxic drugs (long half life in perilymph), noise,

6. Consider high risk: reduced metabolism due to renal/liver dysfunction, elderly and children

5. Ototoxic drugs= often nephrotoxic, hydration is helpful

4. Ototoxicity is dose-dependent and cumulative; avoid bolus dosing,

3. Ototoxicity occurs with various routes: oral, IV, intratympanic, topical skin/body cavity irrigation

2. Ototoxicity can occur even after drug discontinuation

1. ORC-13661 is an oral otoprotective drug - very promising so stay tuned!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