Objectives

- Identify the most common ototoxic medications
- Discuss the ototoxicity mechanism, incidence, and effects for identified medications
- Review preventative strategies to reduce ototoxicity
- Discuss the pharmacogenetics/pharmacogenomics of drug-induced ototoxicity
- Discuss recommendations for audiologic monitoring and follow-up
- Recommend an interdisciplinary approach to prevent and/or monitor when ototoxic medications are prescribed

Drug-Induced Ototoxicity Complications

- QUALITY OF LIFE!!!
  - Tinnitus
  - Vestibular disorders
- Health care expenditures (audiology/MD follow-up, hearing aids, cochlear implant (CI) evaluation/surgery, etc.
  - $200,000 per adult with acquired permanent hearing impairment due to ototoxic medication
  - $1,000,000 per child
- Psychosocial development and education in children
- Social and economic disadvantages

Drug-Induced Ototoxicity - Minich

Ototoxicity Definitions

- Cochlear toxicity: Presents with sensorineural hearing loss (initially affects high frequencies and may be associated with tinnitus)
  - Initial selective damage of cochlear outer hair cells residing in the basal turn
  - Early toxicity is often not identified due to high frequency loss
  - Damage may progress apically and may involve inner hair cells and other cells of the organ of Corti
- Vestibular toxicity: Presents with vertigo and occasionally unsteadiness
  - Patients may have an ataxic gait and lose balance while turning their heads
  - Oculogyric crisis (perception that stationary objects are in motion when moving one's head)
  - Nystagmus
  - Hair cells in the apex of the cristae and the strial regions of the utricular and saccular maculae are damaged (Type 1 hair cells may be more sensitive to ototoxic medications than Type 2 cells)


Ototoxicity Definitions

How Do We Grade Ototoxicity?
Is there a standard?
American Speech and Hearing Association (ASHA) Degree of Hearing Impairment

<table>
<thead>
<tr>
<th>Degree of hearing loss</th>
<th>Hearing loss range (dB HL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10 to 15</td>
</tr>
<tr>
<td>Slight</td>
<td>16 to 25</td>
</tr>
<tr>
<td>Mild</td>
<td>26 to 40</td>
</tr>
<tr>
<td>Moderate</td>
<td>41 to 55</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>56 to 70</td>
</tr>
<tr>
<td>Severe</td>
<td>71 to 90</td>
</tr>
<tr>
<td>Profound</td>
<td>91+</td>
</tr>
</tbody>
</table>

ASHA Ototoxicity Criteria

(A) ≥20 dB decrease in pure tone threshold at one test frequency
(B) ≥10 dB decrease at 2 adjacent test frequencies
(C) Loss of response at 3 consecutive test frequencies where responses were previously obtained


Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Adults)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hearing impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Threshold shift of 15-25 dB averaged at 2 contiguous test frequencies in at least 1 ear</td>
</tr>
<tr>
<td>2</td>
<td>Threshold shift &gt;25 dB averaged at 2 contiguous test frequencies in at least 1 ear</td>
</tr>
<tr>
<td>3</td>
<td>Threshold shift &gt;25 dB averaged at 3 contiguous test frequencies in at least 1 ear; therapeutic intervention indicated</td>
</tr>
<tr>
<td>4</td>
<td>Decrease in hearing to profound bilateral loss (absolute threshold &gt;80 dB HL at 2 kHz and above); non-serviceable hearing</td>
</tr>
</tbody>
</table>

Adults enrolled on a monitoring program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram)

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40
Drug-Induced Ototoxicity - Minich

Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Pediatrics)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hearing Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Threshold shift ≥20 dB at 8 kHz in at least one ear</td>
</tr>
<tr>
<td>2</td>
<td>Threshold shift ≥20 dB at 4 kHz and above in at least 1 ear</td>
</tr>
<tr>
<td>3</td>
<td>Hearing loss significant enough to indicate therapeutic intervention, including hearing aids; threshold shift ≥20 dB at 2 kHz and above in at least 1 ear; additional speech-language related services indicated</td>
</tr>
<tr>
<td>4</td>
<td>Audiologic indication for cochlear implant and additional speech-language related services indicated</td>
</tr>
</tbody>
</table>

*On a 1, 2, 3, 4, 6 and 8 kHz audiogram: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40

Ototoxicity Grades and Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤ 20 dB HL at all frequencies</td>
</tr>
<tr>
<td>1</td>
<td>&gt; 20 dB HL (ie, 25 dB HL or greater) SHHL above 4,000 Hz (ie, 6 or 8 kHz)</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 20 dB HL SHHL at 4,000 Hz and above</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 20 dB HL SHHL at 3,000 Hz or 3,000 Hz and above</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 40 dB, &gt; 45 dB or more SHHL at 2,000 Hz and above</td>
</tr>
</tbody>
</table>

SIOP Boston Ototoxicity Scale

Criteria Limitations

- Variability in hearing loss grading criteria affects reporting of hearing loss incidence
- ASHA criteria may fail to detect significant hearing loss as they assess absolute change in hearing thresholds over time
- Brock criteria in children (developed to evaluate cisplatin-related hearing impairment) does not account for change over time
- National Cancer Institute CTCAE is not in step with ASHA and may underestimate toxicity (often only grade 3/4 toxicity is reported in the literature)
Ototoxic Medications - Which Drugs Should We Look Out For?

How frequently are they used?

Common Ototoxic Medications (Antibiotics)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Drug Class</th>
<th>Cochlear Toxicity (Reversible)?</th>
<th>Vestibular Toxicity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Aminoglycoside</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Aminoglycoside</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Aminoglycoside</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Aminoglycoside</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Aminoglycoside</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Macrolide</td>
<td>Yes (yes)</td>
<td>Yes</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Macrolide</td>
<td>Yes (yes)</td>
<td>Yes</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>Yes (no)</td>
<td>No</td>
</tr>
<tr>
<td>Quinine</td>
<td>Antimalarial</td>
<td>Yes (yes)</td>
<td>No</td>
</tr>
</tbody>
</table>


Common Ototoxic Medications (Chemotherapy)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Drug Class</th>
<th>Cochlear Toxicity (Reversible)?</th>
<th>Vestibular Toxicity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>Platinum analog</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Platinum analog</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
<tr>
<td>Osmoplatin</td>
<td>Platinum analog</td>
<td>Yes (no)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Common Ototoxic Medications (Others)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Drug Class</th>
<th>Cochlear Toxicity (Reversible)?</th>
<th>Vestibular Toxicity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>Loop diuretic</td>
<td>Yes (yes)</td>
<td>No</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Loop diuretic</td>
<td>Yes (yes)</td>
<td>No</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Loop diuretic</td>
<td>Yes (yes)</td>
<td>No</td>
</tr>
<tr>
<td>Salicylates (eg, aspirin)</td>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Yes (yes)</td>
<td>No</td>
</tr>
</tbody>
</table>


Aminoglycosides (AGs)

- Mechanism of action: Interferes with bacterial protein synthesis by binding to the 30s and 50s ribosomal subunits, resulting in a defective bacterial cell wall membrane
- Amikacin, gentamicin, neomycin, streptomycin, tobramycin
- Amikacin, gentamicin, and tobramycin are available as intravenous (IV) medications, and streptomycin is also available as intramuscular (IM) in addition to IV
- Gentamicin (ophthalmic, topical); tobramycin (ophthalmic, oral inhalation); neomycin (oral)
- Primarily used for treatment of gram-negative infections (eg, Pseudomonas aeruginosa and other susceptible gram-negative organisms)
- Hospital-acquired pneumonia, neutropenic fever, cystic fibrosis, treatment of other drug-resistant gram-negative infections

Aminoglycoside Ototoxicity

- Ototoxicity (neurotoxicity) is a boxed warning in the aminoglycoside product labeling
- Risk factors: Preexisting renal impairment, concomitant nephrotoxic/ototoxic medications, advanced age, and dehydration
- Ototoxicity incidence between 3% to 47% (widely variable reports in the literature!!)
- Narrow therapeutic index
- Therapeutic drug monitoring is necessary to monitor and hopefully prevent toxicity
- Dosing mechanisms to reduce toxicity (nephrotoxicity): Once-daily IV dosing allows for a higher peak serum concentration to minimize inhibitory concentration (MIC) ratio and decreased uptake in the renal cortex; aminoglycosides exhibit a postantibiotic effect (persistent suppression of bacterial growth even after drug is no longer present)
Drug-Induced Ototoxicity - Minich

Aminoglycoside Ototoxicity (continued)

- All aminoglycosides may cause cochlear and vestibular toxicity
- Vestibulotoxic agents: Gentamicin and tobramycin (commonly used clinically), streptomycin (rarely used, mostly for drug-resistant tuberculosis)
- Cochleotoxic: Neomycin (not frequently used), kanamycin (not available in the US), and amikacin (commonly used clinically)
- Ototoxicity (in general) tends not to correlate well with serum aminoglycoside concentrations; may be related to total administered dose
- Normal or low serum concentrations do not necessarily mean that ototoxicity will not occur, but elevated concentrations are known to increase ototoxicity risk

Mechanism of Aminoglycoside Ototoxicity

- Not fully elucidated, but . . .
- Role of reactive oxygen species (ROS)
  - Formation of an aminoglycoside-iron complex, which catalyzes the production of ROS from unsaturated fatty acids
  - ROS promote apoptotic and necrotic hair cell death
- Animals overexpressing superoxide dismutase (scavenging enzyme) appear to demonstrate less AG-induced ototoxicity compared with wild-type controls
- Another mechanism: Uptake by sensory cells of the inner ear (likely via receptor-mediated endocytosis)
  - Aminoglycosides are then found in lysosomes; may be protected from degradation due to buffering capacity? Lysosome may eventually rupture, "spilling" cytosolic contents (eg, aminoglycosides)

Mechanism of Aminoglycoside Ototoxicity (continued)

- N-methyl-D-aspartate (NMDA) receptors are present at the synapse between cochlear hair cells and neural afferents
- AGs mimic the positive modulation of polyamines at these receptors, perhaps producing excitotoxic damage
- Administering NMDA antagonists in animal models decrease hearing loss
- High correlation between in vitro receptor activation and relative cochlear toxicity (in humans)
- Gentamicin > tobramycin > amikacin > neomycin
- AGs may also induce structural damage (loss of target innervation and degeneration of spiral ganglion neurons)
Drug-Induced Ototoxicity - Minich

Macrolides

- Mechanism of action: Bind to 50S ribosomal subunit resulting in inhibition of bacterial protein synthesis
- Erythromycin, clarithromycin, azithromycin
- Respiratory tract infections (sinusitis, community-acquired pneumonia [azithromycin, occasionally clarithromycin]), Helicobacter pylori [clarithromycin], otitis media, pharyngitis/laryngitis, skin infections, Lyme disease, etc.
- Azithromycin (probably most clinically utilized macrolide) also may be used in the treatment of chlamydia and gonococcal infections, pelvic inflammatory disease, syphilis, prevention of opportunistic infections in immunocompromised patients (Mycobacterium spp)

Macrolide-Induced Ototoxicity

- Hearing loss, tinnitus, and vertigo
- Typically manifests as bilateral symmetrical hearing loss of 40 to 60 dB within 2 to 7 days of treatment initiation
- Ototoxicity appears to be dose dependent; risk increases with higher doses and serum drug concentrations
- Ototoxicity usually resolves within 1 to 3 weeks of therapy discontinuation
- Occasional reports of irreversible hearing loss (erythromycin, azithromycin)

Mechanism of Macrolide Ototoxicity

- Unclear!
- Some animal studies indicate an effect on outer hair cells (OHCs) and transiently evoked otoacoustic emissions (not consistent from study to study)
- One study showed a reversible reduction of potassium secretion in explanted gerbil cochlea exposed to erythromycin
- Ion transport inhibition in the stria vascularis and the vestibular dark cells may play a role in macrolide-induced ototoxicity
- Which transporters though?
Glycopeptides

- Mechanism of action: Inhibits bacterial cell wall synthesis by blocking glycopeptide polymerization through binding tightly to D-alanyl-D-alanine portion of cell wall precursor
- Vancomycin
  - Treatment of gram-positive (methicillin-resistant) infections: Staphylococcal, streptococcal, enterococcal spp

Vancomycin-Induced Ototoxicity

- Tinnitus and sensorineural hearing loss have been reported
- Early reports perhaps due to product imperfections in the early manufacturing period
- Likely that ototoxicity is due to concomitant administration of other ototoxic drugs (eg, aminoglycosides, loop diuretics)
- Certainly not always possible to avoid concurrent administration of vancomycin with other potentially ototoxic medications, but use with caution when feasible

Quinine-Induced Ototoxicity

- Mechanism of action: Depresses oxygen uptake and carbohydrate metabolism; intercalates into DNA, disrupting the parasite's replication and transcription
- Anti-malarial agent used to treat chloroquine-resistant P. falciparum malaria
- May induce a transient increase in hearing threshold of ~10 dB, but mechanism is not fully understood
- May cause vasoconstriction in the cochlea, leading to decreased cochlear blood flow and reversible alteration of the outer hair cells (in guinea pigs)
- Reduction of hair cell motility
- Effects may be dose dependent (and can occur at therapeutic doses), and affects the high frequency range
- Avoid concurrent use with other ototoxic medications

Cancer Treatment-Associated Ototoxicity

- **Platinum chemotherapy**
  - **Radiation**
    - Doses ≥30 gray to the posterior nasopharynx and mastoid increase risk of developing serous otitis media and associated conductive hearing loss
    - Radiation to the skull may cause bone marrow suppression, which leads to bone marrow hypoxia and hearing loss
  - *Post-auricular hearing loss related to irradiations is generally permanent and progressive* (may be acute or delayed)

- **Surgery involving the ear and auditory nerve**
  - Fluctuations in intracranial pressure due to medical procedures are associated with hearing loss

- **Platinum Chemotherapy Agents**
  - Cisplatin, carboplatin, oxaliplatin
    - Mechanisms of action: Platinum agents covalently bind to DNA and interfere with the function of DNA by producing interstrand DNA cross-links
    - Widely used in cancer treatment (adults and pediatrics)
      - Cisplatin: Bladder, breast, gynecological, head and neck, gastric, lymphomas, multiple myeloma, lymphomas, sarcomas, pancreatic, rectal, colorectal, lung
      - Carboplatin: Bladder, breast, gynecological, head and neck, gastric, lymphomas, sarcomas, pancreatic, rectal, colorectal, lung
      - Oxaliplatin: Colorectal, pancreatic, esophageal, gastric, lymphomas
    - Multiple toxicities
      - Cisplatin: Nephrotoxicity, nausea/vomiting, ototoxicity
      - Carboplatin: Myelosuppression, nephrotoxicity (less than cisplatin), ototoxicity (less than cisplatin)
      - Oxaliplatin: Myelosuppression, neuropathy, hypersensitivity reactions, case reports of ototoxicity

Platinum-Induced Ototoxicity

- **Cisplatin induces sensorineural hearing loss (13% to 95%)**
- **Toxicity**
  - Nephrotoxicity: Loss of renal function
  - Ototoxicity (sensorineural): Loss of hearing function
- **Risk factors**
  - Dose (individual dose and cumulative dose)
  - Duration of infusion: Bolus infusions may be more ototoxic than continuous infusions
  - Younger age (≤4 to 5 years), concomitant cranial irradiation, noise exposure, concurrent ototoxic/nephrotoxic drug administration
  - Pre-existing hearing impairment
- **Hearing impairment**
  - May start days to weeks after treatment (but could be years): Conductive hearing loss
  - Higher frequency hearing loss, but cumulative therapy leads to hearing loss progression in lower frequencies
  - Concurrent chemotherapy, radiotherapy, and other ototoxic drugs and substances

Platinum-Related Sensorineural Hearing Loss

Adult-Onset Cisplatin-Induced Ototoxicity

- Comprehensive audiometric evaluation of cisplatin effects on hearing loss was conducted on 488 adult male germ cell tumor (GCT) survivors
  - Inclusion criteria:
    - Men with a diagnosis of histologically or serologically confirmed GCT
    - <50 years at diagnosis and ≥18 years at study consent
    - Treatment with cisplatin-based chemotherapy
    - No subsequent salvage chemotherapy
  - Audiometric testing: Pure-tone air conduction thresholds bilaterally at frequencies of 0.25 to 12 kHz, otoscopy and bone conduction thresholds (0.25 to 4 kHz) evaluated middle ear function
  - ASHA criteria utilized to classify hearing loss and severity


Adult-Onset Cisplatin-Induced Ototoxicity (Frisina et al 2016 continued)

- Median age at diagnosis: 31 years
- Median interval between chemotherapy and audiometry: 4.25 years
- Median cumulative cisplatin dose: 400 mg/m² (range 198 to 800 mg/m²)
  - Chemotherapy: BEP (60.5%) or EP (32%)
- Median age at diagnosis: 31 years
- Median interval between chemotherapy and audiometry: 4.25 years
- Median cumulative cisplatin dose: 400 mg/m² (range 198 to 800 mg/m²)
  - Chemotherapy: BEP (60.5%) or EP (32%)
- Largely high-frequency sloping hearing loss
  - Only 20% of patients had normal hearing
  - ASHL (25%): moderate (46%), moderately severe (21%), or severe/profound (18%)

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Frisina et al (2016)

Results are from patients in the 28-35 year old age group. The median (blue line) is derived from the normative cohort of men in each patient’s respective age group (20 to 29 or 30 to 39 years). A: Normal hearing; B: Sensorineural; C: Mixed (sensorineural and conductive); D, E, and F sensorineural.

Adult-Onset Cisplatin-Induced Ototoxicity (Frisina et al continued)

- 80% of patients had a hearing loss of >20 dB
- Largest reductions in hearing thresholds occurred at 12 kHz
- Cumulative cisplatin doses > 300 mg/m$^2$ were associated with increased ASHA severity compared with ≤ 300 mg/m$^2$ dose (odds ratio [OR] 1.59; 95% CI 1.14 to 2.21; p=0.0066)
- Moderately severe to profound hearing loss occurred in 39.5% and 44.6% of patients, respectively, with doses ≤ 300 mg/m$^2$ and > 300 mg/m$^2$
- For every 100 mg/m$^2$ increase in cumulative cisplatin dose, a 3.2 dB decline in overall hearing threshold (4 to 12 kHz) occurred (after age adjustment; p<0.001)


Platinum-Induced Ototoxicity (continued)

- Children are more susceptible to platinum-induced ototoxicity than adults
- In pediatrics, a cumulative cisplatin dose > 400 mg/m$^2$ increases the risk of significant hearing loss in the speech frequencies (500 to 2000 Hz)
- Carboplatin cumulative doses > 400 mg/m$^2$ (in children) have been reported to cause ototoxicity
- Children with neuroblastomas and central nervous system (CNS) tumors such as medulloblastoma are at high risk for hearing loss
- Typical neuroblastoma patient is <5 years, receive aggressive cisplatin-based chemotherapy, and may receive high-dose carboplatin chemotherapy in preparation for stem cell transplantation
- Medulloblastoma patients may undergo cranial surgery (with shunt placement), and may receive platinum chemotherapy and CNS radiation

Onset of Platinum-Induced Ototoxicity

- Clinically detectable hearing loss generally requires more than one cycle of treatment to achieve the maximum cumulative dose.
- Knight et al reported a median time of 135 days from start of platinum-based treatment to observation of ototoxicity (evaluated by ASHA criteria); all patients had permanent hearing loss.
- One case series showed progressive hearing loss in pediatric patients with solid tumors receiving platinum chemotherapy occurring as far out as 136 months from the end of therapy.

Mechanism of Platinum Ototoxicity

- Acute and chronic generation of ROS, in addition to DNA damage.
- Increased production of ROS has been illustrated in all 3 subregions of the cochlea (organ of Corti, lateral wall, stria vascularis, spiral ligament, and spiral ganglionic cells).
- Increased ROS production depletes antioxidants (free radical scavengers) such as glutathione-S-transferase (GST), glutathione peroxidase, glutathione reductase, and superoxide dismutase.
- ROS activity also causes increased proinflammatory cytokine formation and superoxide generation in the cochlea.
  - Activation of proapoptotic pathways.

Mechanism of Platinum Ototoxicity (continued)

- Interference with signal transduction from the organ of Corti in the cochlea.
- Magnesium renal wasting due to cisplatin administration affects the ionic composition of the endolymph and perilymph in the stria vascularis, and lowers the threshold for cochlear action potential stimulation.
  - Magnesium also helps to maintain hair cell permeability and cochlear blood flow.
- Damage begins in the first row of outer hair cells at the base of the cochlea (high frequency sounds).
- With increasing doses (or concomitant ototoxic insult), hair cell loss progresses apically to involve the speech frequencies.

Loop Diuretics

- Mechanism of action: Inhibits reabsorption of sodium and chloride in the ascending loop of Henle and proximal and distal renal tubules, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium
- Bumetanide, ethacrynic acid, furosemide, torsemide
- Used for the management of edema associated with heart failure and hepatic or renal disease; acute pulmonary edema
- Loop diuretics may be used in the treatment of hypertension (alone or in combination with other antihypertensives)

Loop Diuretic Ototoxicity

- Hearing loss (generally transient, lasting 30 minutes to 24 hours), but permanent hearing loss has been reported following oral and IV doses of furosemide and ethacrynic acid
- Tinnitus
- Likely dose dependent (many reports occurred following bolus IV injection of higher diuretic doses)
- Risk factors include renal impairment/failure, excessive doses, and concomitant use of other ototoxic medications (eg, aminoglycosides)
- Bumetanide is much more potent than furosemide, but is generally not considered as ototoxic as furosemide and ethacrynic acid (unclear why)
- Bumetanide-associated ototoxicity is usually transient and may occur with rapid IV administration


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Mechanism of Loop Diuretic-Induced Ototoxicity

- Loop diuretics reversibly block Na-K-Cl cotransporters in the thick ascending limb of the loop of Henle.
- Similar transporters are expressed in the inner ear which regulate the ionic composition of the endolymph.
- Decrease the K+ and Cl- concentrations and increase the Na+ and Ca2+ concentrations.
- Loop diuretics cause a dose-related reduction in endocochlear potential (EP).
- Inhibition of the Na-K-ATPase may decrease the EP.


Effect of Route of Administration on Loop Diuretic Ototoxicity

- Dormans et al performed a randomized crossover study of 20 patients with severe heart failure who were long-term users of oral high dose furosemide (at least 250 mg daily).
- Randomized to receive furosemide either as an IV bolus injection (over 5 minutes) or as a continuous infusion (over ~8 hours).
- Plasma and urine samples were obtained at various time points after the start of the infusion to assess furosemide concentrations (plasma) and urine and electrolyte concentrations.
- Patients were then crossed over to the other arm of the study after a brief washout period.
- Data analysis showed that continuous infusion of high dose furosemide caused excretion of a higher volume of urine and electrolytes than a bolus injection, and the maximum furosemide plasma concentration was lower.
- 5 patients reported hearing loss or tinnitus (or both) shortly after bolus injection, but ototoxicity appeared to be transient.


Salicylates

- Mechanism of action: Irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative thromboxane A2, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation; has antipyretic, analgesic, and anti-inflammatory properties.
- Aspirin, magnesium salicylate, salsalate, etc.
- Used for antipyretic, analgesic, and anti-inflammatory purposes (pain, fever, rheumatic conditions, etc.)
Salicylate-Induced Ototoxicity

- High salicylate doses may induce mild to moderate hearing loss
- Hearing loss is typically symmetric and bilateral
- Tinnitus
- Usually resolves within 24 to 72 hours after therapy discontinuation
- Cases of permanent hearing loss have been reported

Mechanism of Salicylate-Induced Ototoxicity

- Rapidly enter the cochlea and diffuse throughout the cochlear duct
- Animal studies illustrated that serum salicylate levels correlated with perilymph salicylate concentrations and hearing loss
- Suppress cochlear function at high and low frequencies and enhance neural activity in the auditory thalamus, cortex, and amygdala
- Cyclooxygenase inhibition decreases prostaglandin production and results in vasoconstriction and reduced cochlear blood flow, thus increasing the permeability and decreasing the mobility of the outer hair cells

Others . . .

- Phosphodiesterase 5 inhibitors (sildenafil, tadalafil, vardenafil) have been associated with hearing loss
- Medications associated with tinnitus:

<table>
<thead>
<tr>
<th>Medications Which May Cause Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
</tr>
<tr>
<td>Carbenoxolone</td>
</tr>
</tbody>
</table>

https://www.uptodate.com/contents/image?imageKey=PC%2F68705&topicKey=PC%2F6855&rank=1~150&source=see_link&search=tinnitus
Aminoglycoside-Induced Ototoxicity (Summary)

- Risk factors for aminoglycoside ototoxicity include preexisting renal impairment, cumulative AG dose (multiple doses or courses of therapy), concomitant nephrotoxic/ototoxic medication administration, older age, dehydration.
- Ototoxicity is generally irreversible.
- Identification of patients at risk is important (eg, patients who have received AGs previously).
- NAC may be an option to prevent ototoxicity in patients on hemodialysis or with end stage renal disease.
- Aspirin may have an otoprotective effect in nondialysis patients receiving AGs, but careful of aspirin dose and side effects (eg, gastrointestinal bleeding).

Macrolide-Induced Ototoxicity (Summary)

- Patients may present with hearing loss, tinnitus, and/or vertigo.
- Ototoxicity may be related to dose.
- Generally presents within a few days of receiving the macrolide antibiotic.
- Transient (usually), some cases of permanent hearing loss have been reported.

Platinum-Induced Ototoxicity (Summary)

- Cisplatin is the most common ototoxic platinum chemotherapy agent, and is used widely in both adult and pediatric cancers.
- Carboplatin may also be ototoxic, but more likely when used after cisplatin has been administered.
- Ototoxicity is irreversible, and may present months to years after chemotherapy completion.
- Early intervention is important!
- Sodium thiosulfate may be an effective strategy for reducing or preventing ototoxicity due to cisplatin (more data to come . . .)
Loop Diuretic-Induced Ototoxicity
(Summary)

- Hearing loss is usually transient, but permanent loss has been reported.
- May be due to IV bolus dosing of high doses of drug (e.g., furosemide).
- Consider continuous infusion of loop diuretic when high doses are necessary.
- Risk factors: Preexisting renal impairment, high loop diuretic doses, and concomitant ototoxic/nephrotoxic medications.

Drug-Induced Ototoxicity
Can we prevent it?

Strategies to Prevent Drug-Induced Ototoxicity

- ROS may play a role in aminoglycoside- and cisplatin-induced ototoxicity.
- Administration of free radical scavengers may be otoprotective.
  - Amifostine
  - N-acetylcyesteine (thiol-containing antioxidant)
  - Vitamin E
  - Sodium thiosulfate, D-methionine, and ebselen
  - Concern: Free radical scavengers may impair the efficacy of the medications, particularly cisplatin.
  - Intratympanic administration of free radical scavengers.

Strategies to Prevent Drug-Induced Ototoxicity (continued)

- Inhibit transporters which selectively mediate uptake of ototoxic drugs into the inner ear
- OCT2 and CTR1 have been shown to transport cisplatin into cells
- Theoretical - OCT2 expressing nonmalignant tissue may be selectively protected from cisplatin-induced toxicity

Preventing Ototoxicity: N-acetylcysteine (NAC)

- Prospective randomized controlled open-label study
- Feldman et al. conducted 53 hemodialysis (HD) patients scheduled to receive gentamicin for dialysis catheter-related bacteremia
- Randomized to receive either NAC (600 mg orally twice daily) or placebo
- Hearing function was assessed at baseline, 1 week and 6 weeks after the completion of gentamicin therapy (pure-tone audiograms over a range of frequencies)

NAC Results (Feldman et al)

<table>
<thead>
<tr>
<th></th>
<th>NAC (N=26)</th>
<th>Control (N=24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audiologic toxicity, patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 (25%)</td>
<td>12 (60%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Early (7-13 days after gentamicin completion)</td>
<td>4 (20%)</td>
<td>11 (55%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Late (42-56 days after gentamicin completion)</td>
<td>2 (10%)</td>
<td>11 (55%)</td>
<td>0.003</td>
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<tr>
<td>Vertigo</td>
<td>4 (20%)</td>
<td>8 (40%)</td>
<td>0.15</td>
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<tr>
<td>Tinnitus</td>
<td>5 (25%)</td>
<td>4 (20%)</td>
<td>0.50</td>
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</table>

NAC Results (Feldman et al)

<table>
<thead>
<tr>
<th></th>
<th>NAC (N=20)</th>
<th>Control (N=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean hearing loss at early follow-up (dB)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA-1</td>
<td>-1.8±4.11</td>
<td>1.3±3.71</td>
<td>0.015</td>
</tr>
<tr>
<td>PTA-2</td>
<td>-0.58±4.46</td>
<td>2.08±4.64</td>
<td>0.072</td>
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<tr>
<td>PTA-3</td>
<td>2.0±3.80</td>
<td>5.8±5.14</td>
<td>0.011</td>
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<tr>
<td><strong>Mean hearing loss at late follow-up (dB)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PTA-1</td>
<td>-0.75±4.27</td>
<td>2.25±6.56</td>
<td>0.095</td>
</tr>
<tr>
<td>PTA-2</td>
<td>0.16±4.32</td>
<td>4.33±8.36</td>
<td>0.095</td>
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<tr>
<td>PTA-3</td>
<td>2.0±5.18</td>
<td>7.0±6.59</td>
<td>0.029</td>
</tr>
</tbody>
</table>

PTA, pure-tone average hearing threshold; PTA-1, PTA at frequencies 250, 500, and 1000 Hz; PTA-2, PTA at frequencies 2000, 3000, and 4000 Hz; PTA-3, PTA at frequencies 6000, 8000, and 12000 Hz


- In the NAC-treated group, there was a statistically significant reduction of ototoxicity compared to the control group (41.6% reduction, p=0.025)
- NAC was primarily protective in the high audiometric frequencies (6000 to 12000 Hz)
- No adverse events related to NAC treatment were observed
- Limitations: Initial hearing test occurred during acute sepsis, single center study, study did not address vestibular ototoxicity by electronystagmography or evaluation of cochlear function by otoacoustic emissions measurement
- Conclusion: NAC may be a simple, safe, and effective medication for prevention of AG-induced ototoxicity in hemodialysis patients
- Applicability to non-HD patients?
Aspirin to Prevent Aminoglycoside Ototoxicity

- Sha et al performed a prospective, randomized double-blind trial in patients receiving gentamicin therapy (daily dosing and a median of 1.5 days).
- Patients were >6 years of age, with multiple exclusion criteria, but patients with preexisting hearing impairment >30 dB at any frequency were excluded.
- 195 patients were randomized to receive otoprotection with aspirin (1 gram three times daily; n=89) or placebo (n=106).
- Ototoxicity was defined as a shift from baseline of ≥15 dB at both 6 and 8 kHz, either unilaterally or bilaterally (assessed 5 to 7 weeks after treatment).
- Incidence of hearing loss in the placebo group was 13%, while in the aspirin group it was 3% (threshold shifts between 15 and 25 dB); p=0.013.
- Gentamicin efficacy was not affected, but gastric symptoms were more common in the aspirin group (3 patients were removed from study due to gastric bleeding).

Amifostine for Cisplatin-Associated Ototoxicity

- Amifostine is a chemoprotectant labeled for the reduction of cisplatin-induced renal toxicity and for the reduction in xerostomia due to radiation therapy in head and neck cancers.
- Mechanism of action: Prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite. The free thiol is available to bind to, and detoxify, reactive metabolites of cisplatin; and can also act as a scavenger of free radicals that may be generated (by cisplatin or radiation therapy) in tissues.

Amifostine for Cisplatin-Associated Ototoxicity (continued)

- A 2016 Cochrane review identified 3 randomized controlled trials and one controlled clinical trial evaluating the use of amifostine for prevention of cisplatin-induced ototoxicity in children.
- Two studies included children with osteosarcoma, and the other study was in children with hepatoblastoma.
- No significant difference in symptomatic ototoxicity (grade 2 or higher) and combined asymptomatic and symptomatic ototoxicity (grade 1 or higher) between receiving treatment with or without amifostine.
- Authors' conclusions: No evidence at this time to support the use of amifostine as an otoprotective strategy in current clinical practice for cisplatin-induced ototoxicity in children.
- In addition, the American Society of Clinical Oncology (ASCO) currently does not recommend amifostine for the prevention of cisplatin-induced ototoxicity.
Vitamin E for the Prevention of Cisplatin-Induced Ototoxicity

- Vitamin E is a major lipid-soluble antioxidant that protects membrane integrity by inhibiting lipid peroxidation
- Maintains neurological structure and function
- Free radical scavenger
- An animal model (rat) suggested that Vitamin E may have a protective effect against cisplatin ototoxicity
- A phase III, randomized, placebo-controlled trial in humans attempted to address Vitamin E’s otoprotective effect

Villani et al (Vitamin E)

- 108 patients with solid malignancies and good functional status were enrolled
- Vitamin E at 400 mg/day orally
- Continued for 3 months after cisplatin discontinuation
- Audiograms and evoked brainstem responses at baseline, 1 month (T1), 2 months (T2), and 3 months (T3)

At the 1 month follow-up, a statistically significant hearing loss was seen at both 2000 Hz (right ear p=0.05; left ear p=0.04) and 8000 Hz (right ear p=0.04; left ear p=0.03) in the control group versus the Vitamin E group
- Audiograms did not show significant changes in the treatment group at 2000, 4000, and 8000 Hz
- Evoked brainstem responses were unchanged in both groups at 1 month
- No data is available on 2- and 3-month follow-up (patients lost to accrual or death)
- Interpretation of results is severely limited due to patient numbers and lack of information on pre- and post-treatment Vitamin E levels
Sodium Thiosulfate (STS) for the Prevention of Cisplatin-Induced Ototoxicity

- Sodium Thiosulfate is a thiol-containing antioxidant which is rapidly excreted by the kidneys after IV administration.
- FDA-approved for the treatment of cyanide poisoning.
- STS inactivated oxygen free-radicals and electrophilic platinum species.
- Animal studies have indicated a positive otoprotective effect on cisplatin ototoxicity.
- Concern for tumor protection (STS may decrease cisplatin cytotoxicity)?
- Delay STS administration until 4 to 8 hours after cisplatin.

STS for Cisplatin-Induced Ototoxicity Prevention (Brock et al)

- SIOPEL 6 was an international, multicenter, prospective, randomized phase III trial in children with standard-risk hepatoblastoma (previously untreated).
- Restricted administration of STS reduce the incidence and severity of cisplatin-induced hearing loss.
- Inclusion/exclusion criteria:
  - Age 1 month to 18 years.
  - No prior chemotherapy.
  - No recurrent disease.
  - No known hypersensitivity to STS.
- Primary outcome measure: Rate of Brock grade ≥1 hearing loss.
- Secondary outcome measures: Response to chemotherapy, overall survival (OS), event-free survival (EFS), chemotherapy toxicity.

STS for Cisplatin-Induced Ototoxicity Prevention (continued - Brock et al)

- Control group received cisplatin alone (60 mg/m² IV on day 1 every 2 weeks for 6 preoperative cycles, and 2 postoperative cycles).
- Patients in the STS group received STS 20 g/m² IV over 15 minutes beginning 6 hours after the completion of cisplatin infusion.
- Audiologic assessments by pure-tone audiometry performed prior to therapy initiation and throughout treatment, as well as in all children who were alive at 3.5 years of age or older.
- Audiograms graded on the Brock scale (grades 0 to 4); trial was developed prior to SIOP Boston ototoxicity grading scale.
STS for Cisplatin-Induced Ototoxicity Prevention (continued - Brock et al)

- 109 patients randomly assigned to STS + cisplatin or cisplatin alone
  - 57 in STS group and 52 in cisplatin alone
- Hearing loss grade 1 occurred in 18 of 55 children (33%) in STS group versus 29 of 46 children (63%) in observation group ($p=0.002$)
- The relative risk of any hearing loss with cisplatin-STS treatment was 0.52 (95% CI, 0.33 to 0.81)
- 48% lower risk of hearing loss with addition of STS versus cisplatin alone
- Serious adverse reactions being possibly, probably, or definitely related to STS included grade 3 infections (2 patients), grade 3 neutropenia (2 patients), grade 3 anemia (1 patient), and tumor progression (2 patients)


STS for Cisplatin-Induced Ototoxicity Prevention (continued - Brock et al)

- Survival analysis (secondary endpoint) showed a 3 year event-free survival (EFS) of 82% in the cisplatin-STS group compared to 79% in the cisplatin alone group (at a median of 52 months of follow-up)
- 3-year overall survival (OS) was 98% versus 92%, respectively
- No statistically significant differences in EFS or OS between the two groups
- STS caused no tumor protection, and did not adversely affect disease outcome
- Administration of STS was associated with a trend toward reduced ototoxicity in all Brock grades
- Caution: STS dose is associated with a high sodium load, and is emetogenic (should prophylaxis with anti-nausea medications)


STS for Cisplatin-Induced Ototoxicity Prevention (continued - Freyer et al)

- ACCL0431 was a multicenter, randomized, open-label, phase 3 trial in children
- Inclusion criteria
  - Age 1 to 18 (newly diagnosed with hepatoblastoma, GCT, medulloblastoma or CNS primitive neuroectodermal tumor, neuroblastoma, osteosarcoma, or other cisplatin-treated cancers)
  - Planned cumulative cisplatin dose >200 mg/m$^2$
  - No previous cisplatin/carboplatin treatment
  - No known thiol sensitivity
  - Normal hearing at baseline

STS for Cisplatin-Induced Ototoxicity Prevention (continued - Freyer et al)

- Patients in the STS group received STS 16 grams/m² IV daily over 15 minutes beginning 6 hours after the completion of cisplatin infusion.
- Control group received cisplatin alone.
- Concurrent use of other ototoxic medications was discouraged.
- Hearing assessments at baseline, up to 8 days before each cisplatin course, 4 weeks after completion of the final course, and 1 year later.
- Audiometric analysis included bilateral pure tone air conduction thresholds at 500 to 8000 Hz, otoscopy, immittance evaluation middle ear function, and evoked otoacoustic emissions (if available).
- Brainstem auditory evoked response thresholds for patients unable to cooperate due to very young age, developmental disability, or medical status.


STS for Cisplatin-Induced Ototoxicity (continued - Freyer et al)

- 125 patients randomly assigned to STS or placebo (n=49 in STS group and n=55 in placebo were assessed for primary endpoint of hearing loss incidence 4 weeks after the final cisplatin dose).
- Hearing loss identified in 14/49 patients (28.6%) in STS group versus 31/55 (56.4%) in observation group (p=0.00022).
- Adjusted for stratification variables, likelihood of hearing loss was significantly lower in STS group compared with the control group (OR 0.31, 95% CI 0.13 to 0.73; p=0.0036).
- STS not associated with severe adverse events.


Survival analysis (secondary endpoint) showed a 3 year event-free survival (EFS) of 54% in the STS group compared to 64% in the control group.

- 3-year overall survival (OS) was 70% versus 87%, respectively.
- Concern for a possible tumor protective effect of STS?
- Possible tumor protective effect against other drugs used in combination with cisplatin.
- A post-hoc analysis showed the inferior outcomes appeared to be limited to patients with disseminated disease.

Corticosteroid receptors are present within inner ear structures. Corticosteroids may upregulate anti-ROS enzymatic activity, reduce inflammation, and decrease ototoxicity-induced inner ear cellular apoptosis. Cisplatin ototoxicity is due, in part, to ROS production and depletion of antioxidant enzymes. Must be careful with use of systemic corticosteroids in cancer patients—utilizing steroids in some disease states may reduce therapeutic efficacy of cancer treatment, or lead to partial treatment in some cancers. Administering corticosteroids (eg, dexamethasone) intratympanically leads to high inner ear concentrations (with minimal systemic absorption). Marshak T et al. Prevention of cisplatin-induced hearing loss by intratympanic dexamethasone: a randomized controlled study. Otolaryngol Head Neck Surg 2014;150(6):983-90. PMID 24618499.

**Intratympanic Dexamethasone for Cisplatin-Induced Ototoxicity**

- Prospective, randomized, controlled study in 26 patients (age ≥ 18 yrs) receiving cisplatin as a component of therapy for cancer (cancer type not specified)
- Baseline evaluation with detailed audiologic history, microscopic otoscopy, pure tone, speech and impedance audiometry, and Distortion Product Otoacoustic Emissions (DPOAEs) testing
- Prior to each cisplatin infusion, intratympanic dexamethasone was administered (0.7 to 1 mL of a 10 mg/mL solution) to the middle ear, while the other ear served as the control
- Follow-up audiometry and DPOAEs were performed 1 week after the cumulative cisplatin dose reached 400 mg/m^2_


**Intratympanic Dexamethasone for Cisplatin-Induced Ototoxicity (Marshak et al)**

- 15/26 patients completed the study; overall results showed a minimal effect of intratympanic dexamethasone for otoprotection from cisplatin-induced hearing loss
- Pure tone threshold at 8000 Hz and pure tone average threshold at 4000 to 8000 Hz significantly increased in both the study (P < .005, P < .03, respectively) and control ears (P < .01, P < .005, respectively)
- Limitations: Small study size, preexisting high tone hearing loss prior to cisplatin administration, optimal timing of administration of intratympanic dexamethasone is difficult to achieve in clinical practice (~40 minutes before infusion).
Intratympanic NAC for cisplatin-induced ototoxicity

- 20 cisplatin-treated patients (ages 16 to 77 years) were eligible for evaluation
- 0.4 to 0.8 mL of NAC (10% solution) was introduced into the middle ear; contralateral ear served as control
- In treated ears, no significant changes in auditory thresholds were observed
- In the control ear, a significant decrease in audition threshold at 8000 Hz was seen (p = 0.008); the changes in auditory thresholds were significantly greater for the control ears versus the treated ears at 8000 Hz (p = 0.005)
- Acute pain reported in all patients, which resolved over ~5 minutes; no other short- or long-term adverse effects were noted
- Chemotherapy efficacy did not appear to be affected, although small patient numbers and nonhomogeneous patient population makes assessment difficult
- More study is needed

Pharmacogenetics of Drug-Induced Ototoxicity

Where do we stand?

- Aminoglycoside Pharmacogenetics
  - A1555G mutation in the mitochondrial genome associated with increased risk for AG ototoxicity
  - Guanine replaces adenine at position 1555 of the mitochondrial 12S rRNA
  - Guanine can form an additional base pair with cytosine at position 1494 of the 12S rRNA, making the mutated rRNA more similar to bacterial 16S rRNA (AG target)
  - AGs bind with higher affinity to the mutated 12S rRNA than to wild type 12S rRNA
  - 10% to 33% of Asian patients who experienced AG ototoxicity carried the 12S rRNA mutation; 17% of Caucasian patients with AG-induced ototoxicity displayed the mutation
  - Overall, incidence of the A1555G mutation (in Caucasian patients) is only 0.2%
Platinum Pharmacogenomics

- Glutathione-S-transferases (GSTs) are a complex group of isoenzymes which catalyze the conjugation of potentially damaging electrophiles with glutathione.
- Glutathione conjugation is thought to be an innate protective mechanism.
- GSTs metabolize environmental pollutants, pesticides, carcinogens, and drugs.
- GSTs are expressed in most tissues in the body (including the brain).
- Genetic polymorphisms have been reported in GSTs, making some individuals more susceptible to disease as well as side effects from medications (e.g., cisplatin-induced ototoxicity).
- Polymorphic proteins GSTM1, GSTT1 and GSTP1 are expressed in the inner ear and have been associated with the development of cisplatin-induced ototoxicity.
- These polymorphisms either decrease or completely eliminate the enzymatic activity of GST.


Platinum Pharmacogenomics (continued)

- Thiopurine S-methyltransferase (TPMT) is an enzyme involved in the metabolism of mercaptopurine, thioguanine, azathioprine.
- Genetic variants in the TPMT gene as well as catechol-O-methyl transferase (COMT) gene may be highly associated with cisplatin-induced ototoxicity.
- DNA samples were collected and genotyped from cisplatin-treated patients in Canada (two cohorts of children who experienced serious ototoxicity were identified).
- COMT risk allele rs9332377 was found in 36 out of 40 patients who had serious cisplatin-induced ototoxicity (p=0.026).
- Combined effect of TPMT rs1220199 and COMT rs9332377 risk alleles was associated with earlier onset and increased severity of cisplatin-induced hearing loss.


But Wait . . .

- Yang 2013 was unable to replicate the findings in Ross 2009
- Investigators evaluated the associations of TPMT and COMT genetic variants with cisplatin ototoxicity in pediatric patients with brain and solid tumors in a single-institution study
- N = 213
- Results showed that hearing loss was related to younger age (p = 0.013) and craniospinal radiation (p = 0.001), but was not associated with TPMT or COMT variants
- Other studies have also reported nonsignificant associations between TPMT variants and cisplatin-induced ototoxicity (Lanvers-Kaminsky 2014; Thiesen 2017)

Platinum Pharmacogenomics – Future Directions

- Organic cation transporter (OCT1 and OCT2) may be involved in the cellular uptake of cisplatin by the kidney
- Animal study (mice) showed that deletion of OCT1 and OCT2 results in significantly altered cisplatin urinary excretion (with no obvious influence on plasma drug levels)
- OCT1 and OCT2 deficient mice had protection from severe cisplatin-induced nephrotoxicity
- Genetic polymorphism in the OCT2 gene (SLC22A2) was associated with reduced cisplatin-induced nephrotoxicity
- OCT2 is also expressed in cochlear hair cells - preventative mechanism to reduce cisplatin-induced ototoxicity?
- OCT1/2 double knockout mice showed signs of ototoxicity and only mild nephrotoxicity after cisplatin treatment compared to wild-type mice

Clinical Practice Recommendations - Cisplatin-Induced Hearing Loss

- Consider pharmacogenetic testing for TPMT variants *3A, *3B, *3C in all pediatric patients who are to receive cisplatin
- Genetic testing to identify patients at risk for cisplatin-induced hearing loss is not recommended in adult patients
- In patients who carry the TPMT *3A, *3B, *3C variants, consider the use of otoprotectants (when applicable), or alternative therapies if possible (e.g., carboplatin). Increased monitoring in patients at high risk for ototoxicity is recommended.
- Issues:
  - Otoprotectants (e.g., sodium thiosulfate) may not be available
  - Carboplatin (or other alternative therapies) may not be acceptable, depending on the type of cancer being treated

Drug-Induced Ototoxicity - Minich

State of the Art - What Does It Mean for Clinical Practice?

- Uneven distribution of genetic variants among patients with or without ototoxicity associated with aminoglycosides and cisplatin
- Underpowered studies may lead to replication failure, as well as differences in the composition of study cohorts (adults versus children, type of tumor/disease studied, etc.)
- Consideration of non-genetic risk factors for ototoxicity is crucial
- Ototoxicity grading differences between grading systems used in various studies limits applicability of study results
- Stay tuned . . . .

When/How Should We Screen for Drug-Induced Ototoxicity?

What can we do if ototoxicity develops?
Audiologic Monitoring (Aminoglycoside)

- High frequency (8 to 20 kHz) pure tone audiometry
- Auditory brainstem response analysis
- Otoacoustic emission testing
- Cost prohibitive??
- Utility?
- Inner ear drug accumulation with aminoglycosides does not appear to occur. However, aminoglycoside concentrations persist in the inner ear tissues for 6 months or longer after administration
- Patient identification: Increased susceptibility to aminoglycoside ototoxicity in patients with a history of previous AG therapy?


Audiologic Screening for Ototoxicity in Cancer Patients

- Report from Children's Oncology Group for late survivorship of childhood cancer
- Perform a complete audiological evaluation at entry into long-term follow-up. If hearing loss is detected, test yearly (at a minimum) or as clinically indicated. If audiogram is inconclusive, consider electrophysiologic testing (e.g., otoacoustic emissions)
- Complete audiological evaluation includes pure tone air and bone conduction, speech audiometry, and tympanometry for both ears
- Frequency-specific auditory brainstem response (ABR) may be performed if the above evaluation is inconclusive


Screening for Platinum-Based Ototoxicity

- In young children (< 5 years), baseline and ongoing auditory monitoring is recommended (before therapy starts and then every 1 to 2 cycles of platinum-based therapy thereafter)
- For older patients, less frequent testing may be sufficient, but all patients receiving potentially ototoxic therapy should receive audiologic screening at baseline and at the completion of therapy (at a minimum)

Drug-Induced Ototoxicity - Minich

Intervention in Children with Hearing Loss

- Speech and language therapy
- Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical issues
- Refer patients to school liaison or cancer center to facilitate educational interventions
- Amplification technology, hearing aids, cochlear implants


Interdisciplinary Approach to Drug-Induced Hearing Loss

- Physicians, pharmacists, nurses aware of potential drug-induced ototoxicity
- Referral to audiology for baseline audiometric evaluation
- Audiologic follow-up as needed to assess degree of hearing loss
- Interventions: hearing aids, assistive technology, cochlear implants
- Otolaryngology follow-up as needed
- Social work, school counselor, etc. involvement is also crucial for pediatric patients with hearing impairment
- Issues
  - Timeliness (identifying patients at risk, referral early rather than later)
  - Practicality (inpatient versus outpatient, clinical status of patient)
  - Availability of diagnostic (audiometric tests, audiology, pharmacogenetic screening, otoprotectants)

Summary

- Drug-induced ototoxicity is a complication that may significantly impact patients’ quality of life, education, economic, and social status
- Awareness of which drugs or classes of medications cause ototoxicity is crucial
- Early identification of ototoxicity and an interdisciplinary approach to identifying, monitoring, and managing drug therapy and ototoxicity is important
QUESTIONS? COMMENTS?

THANK YOU!!

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