Ototoxicity Update: Assessment, Monitoring & Prevention

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Ototoxicity Update: Assessment, Monitoring & Prevention

- PubMed Search January 7, 2017 (www.nlm.nih.gov) for "ototoxicity" = 3949 peer-reviewed publications
- Potentially Ototoxic Drugs
- Mechanisms of Ototoxicity
- Factors Influencing Ototoxicity
- Assessment and Monitoring of Ototoxicity
- Management and Prevention of Ototoxicity
- Conclusions

Ototoxicity Update: Assessment, Monitoring & Prevention

- Lanvers-Kaminsky et al (2016). Drug-induced ototoxicity: Mechanisms, pharmacogenetics, and protective strategies. *Clinical Pharmacology Therapy*, Dec 21
- Knight et al (2016). Group-wide prospective study of ototoxicity assessment in children receiving cisplatin chemotherapy. *Journal of Clinical Oncology,* Dec 12
- Van As et al (2016). Platinum induced hearing loss after treatment for childhood cancer. *Cochrane Database Syst Rev*, Aug 3
- Lestner et al (2016). Vancomycin toxicity in neonates: A review of the evidence. *Curr Opin Infect Dis, 29:* 237-247
- Crundwell et al (2016). Ototoxicity classifications: A review. *International Journal of Audiology, 55*, 65-74

Ototoxicity Update: Assessment, Monitoring & Prevention

- Hall JW III, Winkler JB, Herndon DN, Gary LB (1986) Auditory brainstem response in young burn wound patients treated with ototoxic drugs. *International Journal of Pediatric Otorhinolaryngology 12*: 187-203
- Hall JW III, Winkler JB, Herndon DN, Gary, LB (1987). Auditory brainstem response in auditory assessment of acute severely burned children. *Journal of Burn Care and Rehabilitation 8:* 195-198
- Hall JW III (2000). *Handbook of Otoacoustic Emissions*. San Diego: Singular Publishing
- Hall JW III (2014) *Introduction to Audiology Today*. Boston: Pearson Educational

Ototoxicity Update: Assessment, Monitoring & Prevention

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Ototoxicity Update: *Potentially Ototoxic Drugs*

- Platinum Complexes
  - Anti-neoplastic drugs
  - Cis-platin, Carboplatin, others
  - Permanent bilateral hearing loss (> 50% of all patients and > 60% of pediatric patients)
- Aminoglycoside Antibiotics (discovered in 1940s)
  - Bacterial infections
  - Tobramycin, gentimicin, amikacin, others
  - Permanent hearing loss in 2 to 20% of patients
- Other Antibiotics
  - Vancomycin, erythromycin, others

Ototoxicity Update:
Potentially Ototoxic Drugs

- Loop Diuretics
  - Renal failure, hypertension, congestive heart failure, etc
  - Furosemide (Lasix), ethacrynic acid, bumetanide
- Antimalarial Drugs
  - Quinine, many others
- Salicylates
  - Aspirin
  - Non-steroidal anti-inflammatory drugs
- Environmental Agents and Substances
  - Mercury
  - Solvents

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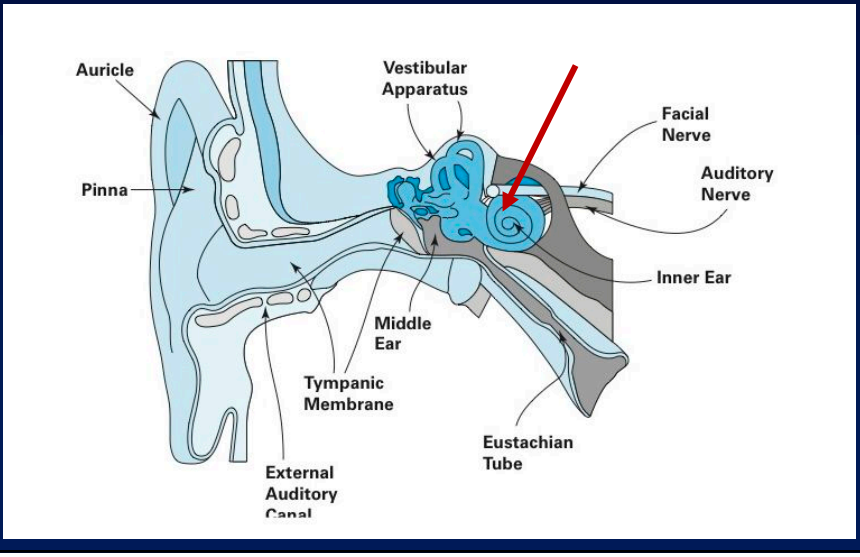
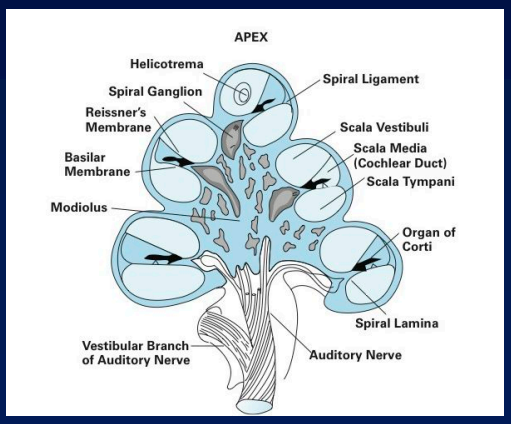
Ototoxicity Update: Assessment, Monitoring & Prevention

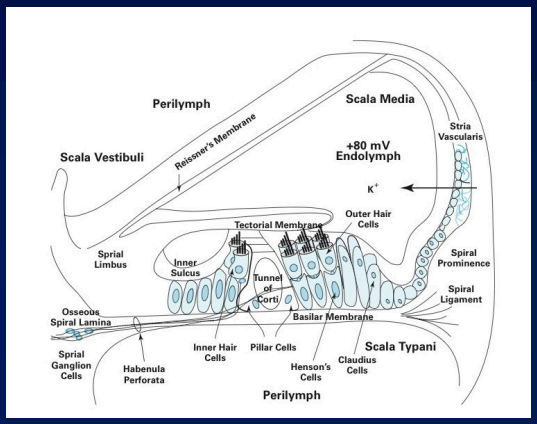
(Figure from Hall JW III. *Introduction to Audiology Today*. Boston: Pearson Educational, 2014)



Ototoxicity Update: Assessment, Monitoring & Prevention

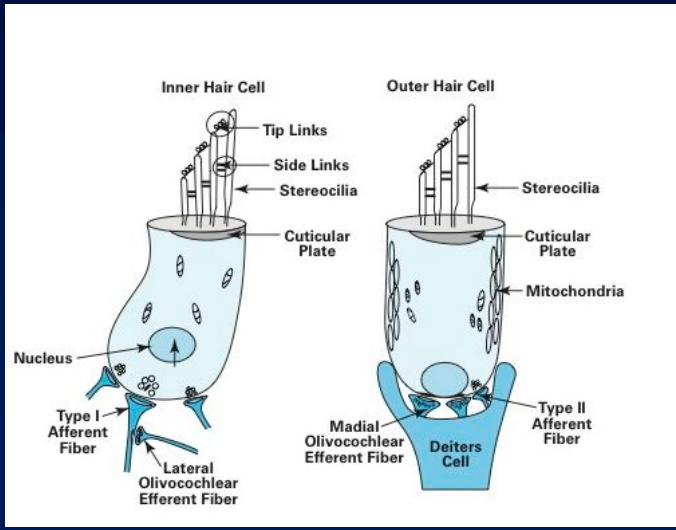
(Figure from Hall JW III. *Introduction to Audiology Today*. Boston: Pearson Educational, 2014)





Ototoxicity Update: Assessment, Monitoring & Prevention

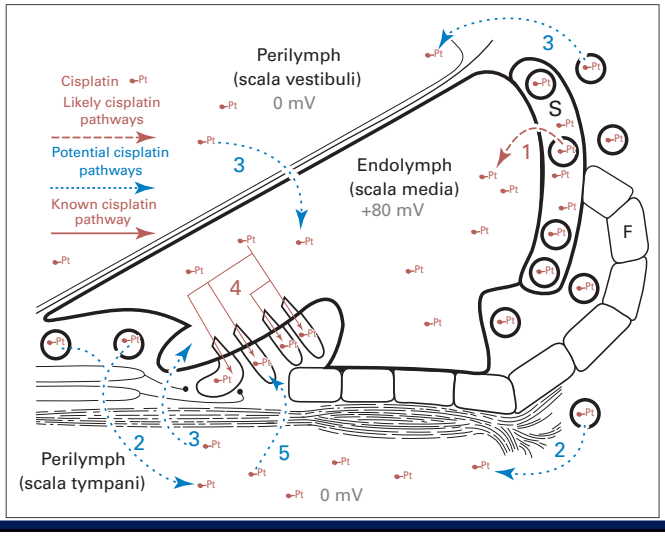
(Figure from Hall JW III. *Introduction to Audiology Today*. Boston: Pearson Educational, 2014)



Ototoxicity Update: *Mechanisms of Ototoxicity*

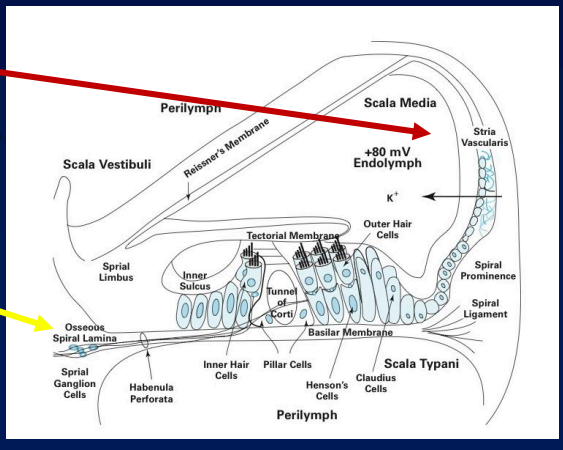
- Dose dependent death of cochlear hair cells
- Cochlear hearing loss
  - Basal (high frequency) region first affected with progression to lower frequencies
  - High frequencies are critical for speech perception and language acquisition
- Sensory hearing loss is usually bilateral
- Greatest risk for young children
- Drugs (e.g., cisplatin) in mitochondria trigger release of toxic amounts of reactive oxygen species (ROS)
- Increased ROS disrupts hair cell metabolism and function

Ototoxicity Update:
Mechanisms of Ototoxicity (Cisplatin)
From Brock et al. Journal of Clinical Oncology 30, 2012

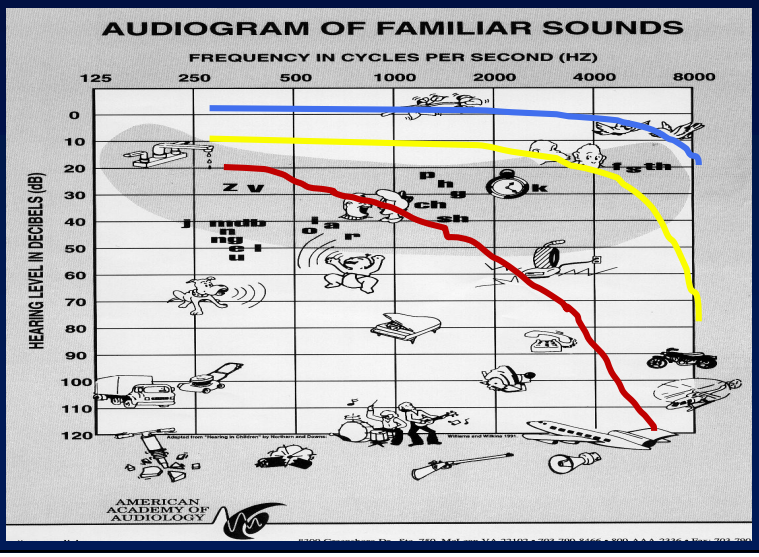


Ototoxicity Update:
Mechanisms of Ototoxicity

- Selected drugs (e.g., cisplatin & furosemide) produce degeneration of stria vascularis
- Decrease in the endocochlear potential
- Dysfunction of spiral ganglion cells



Ototoxicity Update:
Ototoxicity Induced Progressive High Frequency Hearing Loss



Ototoxicity Update:
Mechanisms of Ototoxicity (2)
Brock et al, J Clin Oncology, 30, 2012

- Ototoxicity is characterized by considerable inter-individual variability, e.g.,
  - Cisplatin does not affect auditory function in ~20% of children
- Genetic factors influence susceptibility to drugs (e.g., cisplatin)

Table 1. Results of Published Studies in Cisplatin Pharmacogenomics Using Candidate Gene Approach

Gene/Protein	Summary of Results
Megalin	Selected for candidate gene approach because it is highly expressed in renal proximal tubular cells and marginal cells of the inner ear. Also associated with the uptake of ototoxic aminoglycosides.[46]
GSTs	Animal studies suggest GSTs are found in the cochlea and have a role in protection from ototoxicity. The *GSTM1*, *GSTT1*, and *GSTP1* genes are polymorphic in humans, and nonfunctional variants are commonly found in whites.[47]
TPMT, *COMT*	Two cohorts (identified through the Canadian Pharmacogenomics Network for Drug Safety) were evaluated for cisplatin toxicity.[42] They used a gene chip composed of variants in 220 drug metabolism genes and found that genetic variants of *TPMT* (odds ratio, 17) and *COMT* (odds ratio, 5.5) were significantly associated with cisplatin-induced hearing loss. The combination of *TPMT* and *COMT* genotypes could be used as a clinical test to identify those who will have cisplatin-induced deafness with a positive predictive value of 92.9% and a negative predictive value of 48.6%.[42] Mechanisms of toxicity include increased efficiency of cisplatin cross-linking, as well as a possible role of the methionine pathway through a common substrate, *S*-adenosylmethionine.[42]
ERCC1, *ERCC2*	*ERCC1* encodes an excision repair enzyme involved in platinum DNA adduct repair.[48] Two common single nucleotide polymorphisms in *ERCC1* are correlated with an increased risk of both toxicity and survival in adults with non–small-cell lung tumors.[49,50]
Mitochondrial gene mutations	No studies have been performed that have evaluated for associations between mitochondrial gene mutations and cisplatin-induced hearing loss. Aminoglycoside-induced deafness is thought to be associated with mutations in the mitochondrial 12S ribosomal RNA gene.[51-53]

Abbreviations: *COMT*, catechol-*O*-methyltransferase; *ERCC1*, excision repair cross-complementation group 1; *ERCC2*, excision repair cross-complementation group 2; GST, glutathione-*S*-transferase; *TPMT*, thiopurine *S*-methyltransferase.

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Ototoxicity Update: *Factors Influencing Ototoxicity*

- Genetics
- Specific drug
- Dosage
- Peak serum levels
- Prior or simultaneous exposure to other ototoxic drugs
- Exposure to noise
- Age (youngest children most vulnerable)
- Renal function and toxicity
- Conclusion: Ototoxicity is variable among patients and cannot be predicted with certainty. Ototoxicity is detected only with monitoring of auditory function.

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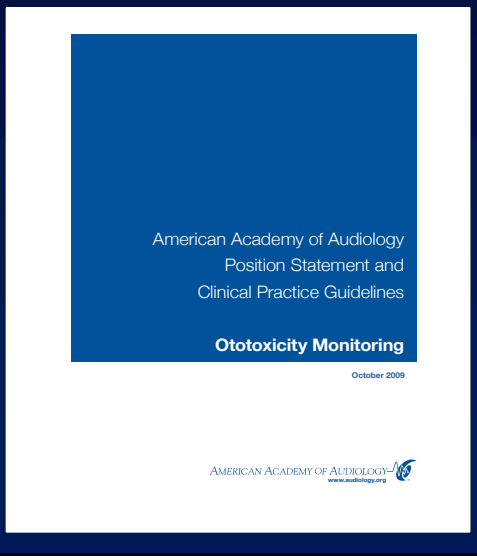
Clinical Practice Guidelines for Ototoxicity Assessment and Monitoring *(American Academy of Audiology, 2009)*



- Task Force Members
  - John Durrant (Chair)
  - Kathleen Campbell
  - Stephen Fausti
  - O'Neil Guthrie
  - Gary Jacobson
  - Brenda Lonsbury-Martin
  - Gayla Poling

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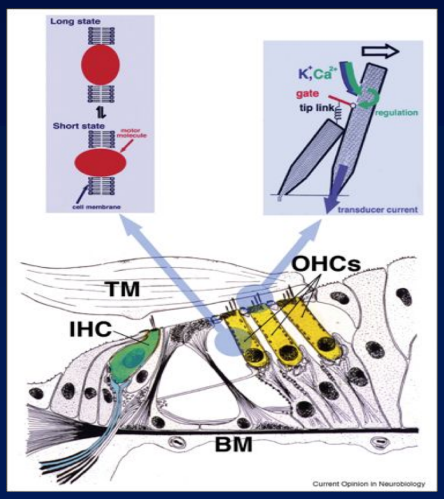
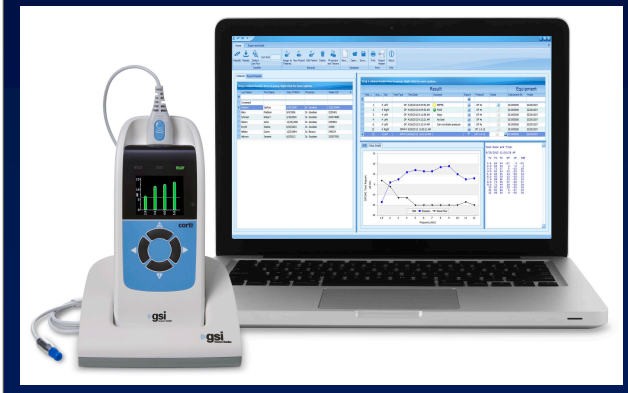
American Academy of Audiology Clinical Practice Guidelines for Ototoxicity Monitoring (2009)

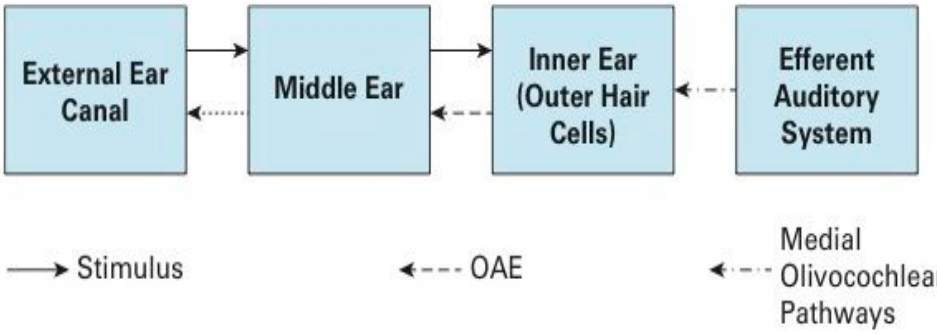
- Assessment and Monitoring Techniques
  - Pure tone audiometry
    - ✓Conventional test frequencies (250 – 8000 Hz)
    - ✓High frequency audiometry or HFA (> 8000 Hz)
  - Distortion product otoacoustic emissions (DPOAEs)
    - ✓Determine reliability during baseline measurement
    - ✓High frequency protocol with many frequencies/octave
  - Frequency-specific electrophysiological measures as indicated
    - ✓ABR (tone burst and chirp stimuli)
    - ✓ASSR

Otoacoustic Emissions (OAEs): Sounds Detected in the Ear Canal Reflecting Outer Hair Cell Motility

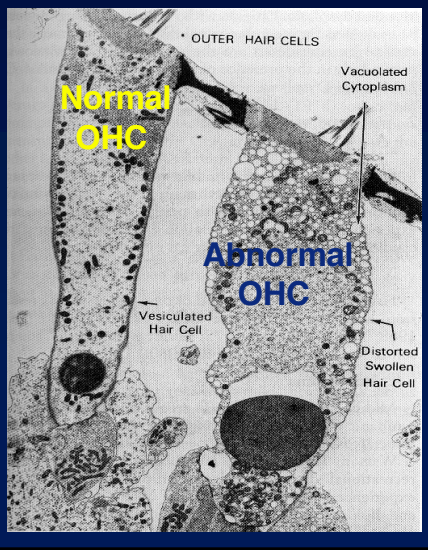




Measurement of Otoacoustic Emissions (OAEs)



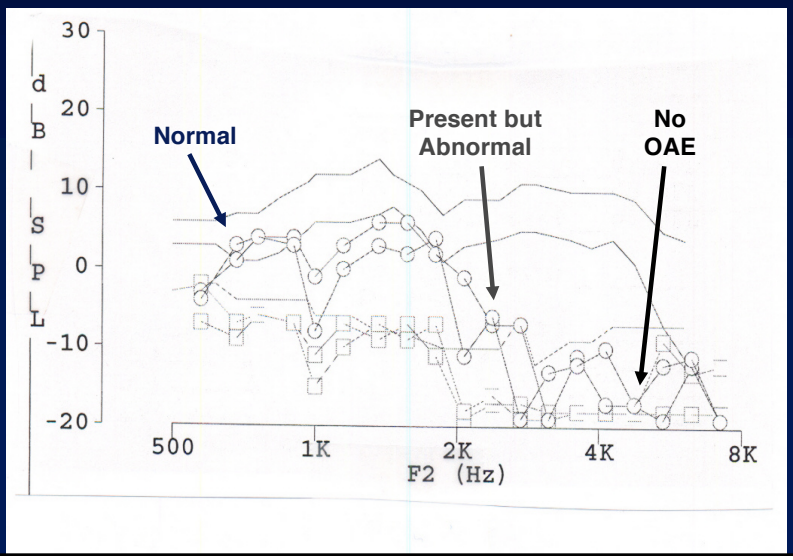
OAEs in Early Detection of Outer Hair Cell Dysfunction: *Rationale Underlying Many Clinical Applications*



Auditory Anatomy Involved in the Generation of OAEs: *Ototoxicity Affects Outer Hair Cells and Stria Vascularis*

- Outer hair cell motility
  - Prestin motor protein
- Stereocilia
  - Motion
  - Stiffness
- Tectorial membrane
- Basilar membrane mechanics
  - Dynamic interaction with outer hair cells
- Stria vascularis
- Middle ear (inward and outward propogation)
- External ear canal
  - Stimulus presentation
  - OAE detection

Analysis of Distortion Product Otoacoustic Emissions (DPOAEs)



2007 Joint Committee on Infant Hearing (JCIH): Protocol for Evaluation for Hearing Loss In Infants from Birth to 6 Months

- Child and family history
- Evaluation of risk factors for congenital hearing loss
- Parental report of infant's responses to sound
- Clinical observation of infant's auditory behavior
- Audiological assessment
  - Auditory brainstem response (ABR)
  - Otoacoustic emissions (distortion product or transient OAEs)
  - Tympanometry with 1000 Hz probe tone
  - Supplemental procedures, e.g.,
    - ✓Electrocochleography (ECochG)
    - ✓Auditory steady state response (ASSR)
    - ✓Acoustic reflex measurement (for 1000 Hz probe tone)

OAEs in Monitoring For Ototoxicity: Recording and Analysis

- Utilize distortion product otoacoustic emissions versus TEOAEs to reach higher frequency region
  - Record to highest available test frequencies (≥ 12 K Hz)
  - Sensitive stimulus intensity levels (L1 = 65 dB; L2 = 55 dB)
  - Use multiple frequencies/octave (> 5)
  - Replicate DPgrams to determine normal variability
- Analysis
  - Verify the presence of DPOAEs for each frequency
  - Analyze DP amplitude relative to normal region
  - Compare average amplitude for replications for baseline versus post-drug recordings
  - Report any decrease in amplitude exceeding variablity

OTOTOXICITY:
Rationale for Monitoring with DPOAEs (*not* TEOAEs)

- Highly sensitive to cochlear (outer hair cell) dysfunction
- Most ototoxic drugs first damage outer hair cells
  - Aminoglycosides (e.g., gentamicin)
  - Loop diuretics (lasix or furosemide)
  - Cisplatin
- Objective (can be performed on sick patients)
- Brief test time (one or two minutes)
- High degree of frequency detail (selectivity) with information on many frequencies within each octave
- High frequency limit up to 12,000 Hz with DPOAEs (TEOAE limit is about 5000 Hz)
- Earlier detection of cochlear dysfunction vs. audiogram

Selected Clinical Applications of OAEs in Pediatric Populations
(See Chapter 9 in Dhar & Hall, 2012)

- Pediatric Applications
  - Infant hearing screening
  - Diagnosis of auditory dysfunction in infants and young childre
    - Confirm or rule out outer hair cell dysfunction
    - Identification of ANSD
  - Monitoring ototoxicity
  - Pre-school/school screenings
  - Identification of pseudohypacusis

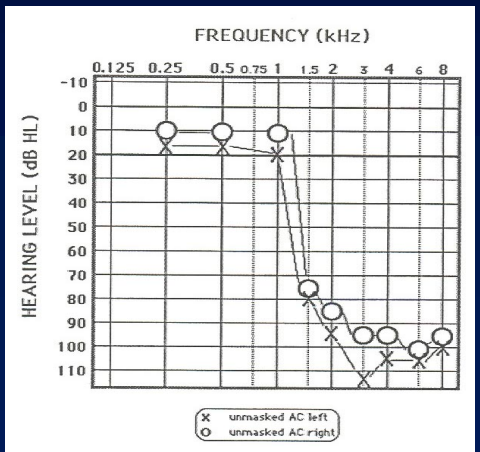
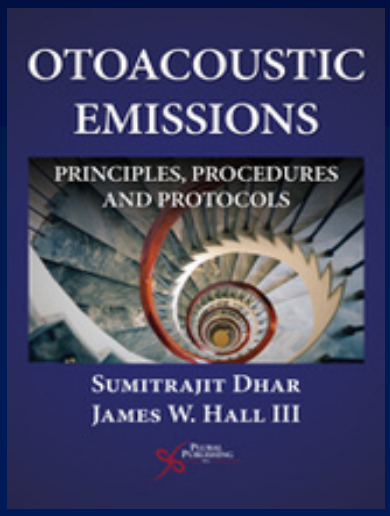


FIG. 1. This 24-year-old woman with cystic fibrosis received frequent tobramycin therapy since her diagnosis at the age of 3 months. Her audiogram shows a hearing loss at high frequencies.

An Up-to-Date and Understandable Resource on Otoacoustic Emissions



Dhar S & Hall JW III
Plural Publishing
(www.pluralpublishing.com)
150 pages, Softcover, 5 x 7.5"
ISBN10: 1-50756-342-0
ISBN13: 978-1-59756-342-0
$45.00

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Ototoxicity Update:
Ototoxicity Scales, Grades and Classification

- Documentation and classification of the degree of hearing loss
- Approach #1: Change of hearing from baseline
  - World Health Organization (WHO) Common Toxicity Criteria, 2007
  - National Cancer Institute Common Terminology-Criteria for Adverse Events (NCI-CTCAE), 2010
  - Children's Cancer Group A9961 (CCG-A9961)
  - Children's Hospital Boston (CHB) Scale, 2009

Ototoxicity Update:
Ototoxicity Scales, Grades and Classification

- Approach #2: Absolute hearing loss in children
  - Brock Scale, 1991
  - Brock & Chang, 2010
  - International Society of Pediatric Oncology (SIOP) Boston Scale, 2012
    - ✓Used at the end of a clinical trial of treatment
    - ✓Sensitive to high-frequency hearing loss
    - ✓Uses criteria corresponding to functional outcomes, e.g., need for audiologic interventions (hearing aids and other assistive technologies)
    - ✓Baseline evaluation is "gold standard" and recommended
    - ✓Recognizes that baseline is not always possible

Ototoxicity Update:
SIOP Boston Ototoxicity Scale
Brock et al, J Clin Oncology, 30, 2012

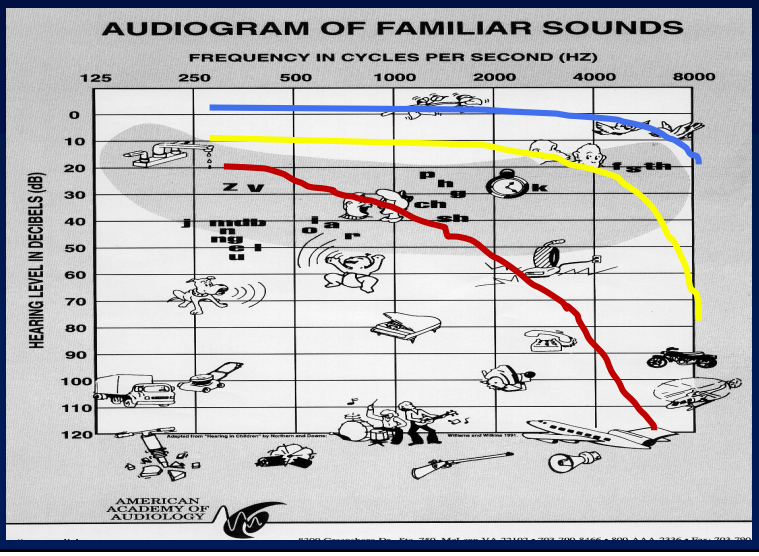
Table 2. SIOP Boston Ototoxicity Scale

Grade	Parameters
0	≤ 20 dB HL at all frequencies
1	> 20 dB HL (ie, 25 dB HL or greater) SNHL above 4,000 Hz (ie, 6 or 8 kHz)
2	> 20 dB HL SNHL at 4,000 Hz and above
3	> 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	> 40 dB HL (ie, 45 dB HL or more) SNHL at 2,000 Hz and above

NOTE. Scale is based on sensorineural hearing thresholds in dB hearing level (HL; bone conduction or air conduction with a normal tympanogram). Bone conduction thresholds are used to determine the grade in the case of abnormal tympanometry and/or suspected conductive or mixed hearing loss. Even when the tympanogram is normal, bone conduction is strongly recommended at the single frequency that is determining the ototoxicity grade to fully confirm that the hearing loss at that frequency is sensorineural. Temporary, fluctuating conductive hearing loss due to middle ear dysfunction or cerumen impaction is common in the pediatric population, and decreases in hearing thresholds that include conductive hearing losses do not reflect ototoxicity to the cochlea.

Abbreviations: SIOP, International Society of Pediatric Oncology; SNHL, sensorineural hearing loss.

Ototoxicity Update:
Impact of *Ototoxicity Induced Hearing Loss in Children*



Ototoxicity Update: Consequences of Hearing Loss in Young Children

- Delayed and disrupted speech and language acquisition
- Poor communication skills
- Psychosocial responses to hearing loss
- Academic underperformance
- Reading delays and disorders
- Long-term consequences
  - Academic failure
  - Unemployment or under-employment
  - Poor quality of life

Ototoxicity Update: *Management and Prevention*

- Management of hearing loss in young children
  - Family centered counseling
    - ✓Informational counseling
    - ✓Personal adjustment counseling
  - Hearing aids as indicated
  - Other hearing assistive technology
  - Monitoring of hearing status with adjustments in management as indicated

Ototoxicity Update:
Prevention of Ototoxicity (Otoprotection)

- Animal studies
  - Antioxidants
    - ✓Glutathione (inhibits platinum DNA binding but reduces chemotherapeutic efficacy)
    - ✓Many other antioxidants may offer otoprotectin without compromising anticancer therapy
  - Delivery methods
    - ✓Intravenous or intra-arterial
    - ✓Localized delivery to ear via round window
    - ✓Simultaneous administration of otoprotectant

Ototoxicity Update:
Prevention of Ototoxicity or Otoprotection
(Brock et al, 2012)

- Clinical studies
  - Antioxidants
    - ✓Amifostine
    - ✓Sodium thiosulfate (STS)
  - Requirements for oto-protectants
    - ✓Effective protection of cochlear function
    - ✓Do not interfere with therapeutic efficacy
    - ✓Minimal adverse effects
    - ✓Simple administration
    - ✓Suitable for use with various drugs
    - ✓Attractive to pharmaceutical industry

Ototoxicity Update:
Otoprotection for Ototoxicity
Brock et al, J Clin Oncology, 30, 2012

Table 3. Representative Emerging Otoprotectants for Use With Platinum-Based Chemotherapy

Agent	Route	Mechanism	Comment
STS	IV	Thiol-reducing agent	In rats, STS protects against ototoxicity[14] without reducing antitumor efficacy.[101] Currently in phase III trials. Possible approaches include delayed administration, [14,87,100] two-compartment models, [4,5,104] and cochlear application.[85,96]
Amifostine	IV	Metabolized to WR-1065, a thiol-reducing agent	Most trials show no otoprotection; dose intensity may be critical; routine use of amifostine to prevent platinum-associated neurotoxicity or ototoxicity is not currently supported by the American Society of Clinical Oncology 2008 Clinical Practice Guideline.[105]
NAC	IV	Thiol-reducing agent	High dose (1,000 mg/kg) IV or intra-arterial NAC protects against cisplatin ototoxicity in the rat when given either 30 minutes prior to or 4 hours after chemotherapy and also blocks kidney toxicity and weight loss.[14,78] Delayed IV NAC does not block chemotherapy antitumor efficacy.[101]
D-methionine	PO, IV, or delivery to the round window	Glutathione modulator, free-radical scavenger	Animal studies have confirmed D-methionine protection from carboplatin- and cisplatin-induced ototoxicity.[99] Effective delivered PO,[99] systemically, or to the round window.[96] Animal studies have not shown significant antitumor interference.[106] One small-scale clinical trial showed complete otoprotection.[107] Larger-scale clinical trials will be needed.
Ebselen	PO	Glutathione peroxidase promoter	In animal studies, ebselen, a selenium-containing compound, has reduced cisplatin-induced outer hair cell loss with and without allopurinol co-administration[89] and does not appear to comprise cisplatin's antitumor efficacy.[108] To date, ebselen has not been tested in clinical trials, but trials are in the planning stages.
Ringer's solution or dexamethasone	Intratympanic injection	Agent dependent (anti-inflammatory)	Compartmental therapy via tympanostomy tubes.[92,95]

Abbreviations: IV, intravenous; NAC, N-acetylcysteine; PO, orally; STS, sodium thiosulfate.

Ototoxicity Update:
Proposed Protocol for Audiological Assessment and Monitoring at AUBMC … Young Children

Ototoxicity Update:
Proposed Protocol for Audiological Assessment and Monitoring at AUBMC

- Infants and young children
  - Baseline (whenever possible) or initial assessment
    - ✓Distortion product OAEs (2000 to ≥ 8000 Hz)
    - ✓Tympanometry (1000 Hz probe tone < 6 months)
    - ✓Acoustic reflex with broadband noise (BBN), low frequency noise band (NB), high frequency NB
    - ✓Auditory brainstem response (ABR) or auditory steady state response (ASSR) for 4000 and 8000 Hz
  - Monitoring protocol
    - ✓Distortion product OAEs (2000 to ≥ 8000 Hz)
    - ✓Assessment if DPOAE changes are detected
  - Vestibulotoxicity assessment as indicated

Ototoxicity Update:
Proposed Protocol for Audiological Assessment and Monitoring at AUBMC … Older Children and Adults

Ototoxicity Update:
Proposed Protocol for Audiological Assessment and Monitoring at AUBMC

- Older children and adults
  - Baseline (whenever possible) or initial assessment
    - ✓Distortion product OAEs (2000 to ≥ 8000 Hz)
    - ✓Tympanometry (1000 Hz probe tone < 6 months)
    - ✓Pure tone audiometry for conventional and high frequencies (250 to 16000 Hz)
    - ✓Word recognition performance
  - Monitoring protocol
    - ✓Distortion product OAEs (2000 to ≥ 8000 Hz)
    - ✓Full assessment if DPOAE changes are detected
  - Vestibulotoxicity assessment as indicated

Thank You!
Questions?