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26th Mayo Clinic Audiology Conference
February 6, 2016

“The best interest of the patient is the only interest to be considered.”
- William J. Mayo, M.D.

Ototoxicity
- Certain exposures to medications/chemicals can damage the ear, resulting in hearing loss, ringing in the ear, or balance disorders
- May progress unnoticed by the patient until a communication problem becomes apparent
- Early intervention becomes critical for the maintenance of quality of life
  - Address communication needs while reducing the long-term impacts of hearing loss
Ototoxicity

• A large number of therapeutic substances and industrial chemicals can cause ototoxicity
  • Over 200 medications are reported to be potentially ototoxic
  • Nine million Americans are exposed to ototoxic chemicals

Ototoxicity Monitoring

• WHO?
• WHAT?
• WHERE?
• WHEN?
• WHY?
Role of Audiology

- Adapted from http://education.healthcaresource.com/
Delayed Identification
Speech and Language Development
Reasoning Skills
Educational Achievement
Social-Emotional Development
Lifetime of Medical Expenses

Pediatric Considerations

Increased risk with cisplatin dose

n=73
Ages: 0 to 20 years
Veterans\textsuperscript{10-11}

- Treatment with cisplatin can result in permanent cochlear damage in up to 50% of patients
- New tinnitus onset in ~40% of patients

Impacts\textsuperscript{4-8}

- Speech Communication
- Coping Skills
- Stress
- Emotional Well-Being
- Quality of Life
- Delayed Identification
- Speech and Language Development
- Reasoning Skills
- Educational Achievement
- Social-Emotional Development
- Lifetime of Medical Expenses

Otoxicity Monitoring

WHAT?
Ototoxic Agents

- Amikacin
- Gentamicin* 
- Neomycin* 
- Kanamycin 
- Nalidixacin 
- Streptomycin* 
- Tobramycin* 

Aminoglycoside Antibiotics

- Ethacrynic acid* 
- Furosemide* 
- Bumetanide* 

Loop Diuretics

- Aspirin 
- Nonsteroidal anti-inflammatory agents 
- Pyrimethamine 

Antimalarial Drugs

- Quinine* 
- Chloroquine 
- Hydroxychloroquine* 
- Primaquine* 
- Quinidine* 
- Pyrimethamine 

Salicylates

- Cisplatin 
- Carboplatin 
- Oxaliplatin 
- Methotrexate* 
- Vincristine 
- Dactinomycin 

Antineoplastic Drugs

*Also possibly vestibulotoxic

Aminoglycoside Antibiotics

- Common populations: 
  - Neonatal sepsis 
  - Gram-negative bacterial infections 
  - Cystic Fibrosis 

- Hearing loss estimated in 2-20%4,12-13

- Cochlear and vestibular hair cells and vulnerable4

Platinum-based Chemotherapy

- Carboplatin 
  - Treatment for lung, head and neck, and ovarian cancers 
  - Risk in combination with cisplatin or at high dose levels4

- Cisplatin 
  - Treatment for testicular, ovarian, head and neck, cervical, bladder, brain, and lung cancers 
  - Hearing loss occurs in 40-60%4,10,14 
  - Ototoxicity is recognized as a severe, dose-limiting side effect14 
  - Impacts outer hair cells first14
Cranial Radiation Therapy

- Can be in combination with surgery or chemotherapy
- Increased risk of hearing loss from radiation to head and neck
  - Radiation to the posterior fossa
- Radiation-induced hearing loss
  - 40% acute middle ear complications
- Progressive hearing loss up to 10 years post
  - Late onset hearing loss

Ototoxicity Monitoring

WHERE?

Impacts on the Auditory System

- Impacts the structure and function of:
  - vestibular & cochlear hair cells and their supporting structures
  - the vestibulocochlear (VIIIth) nerve

Adapted from MC4324rev1115 and Dallos & Fakler, 2002
Symptoms

• Hearing Loss
  • Permanent or temporary
  • Varying degree and configuration
  • Progressing from high to low frequencies

• Tinnitus ("ringing in the ears")
• Aural fullness/pressure
• Imbalance/dizziness

Ototoxicity

• Difficult to predict; poorly correlated with:
  • Dosage
  • Peak serum levels
  • Development of other toxicities (renal toxicity)

• Depends on dosage, age, genetics, and concurrent exposure to noise or other chemicals/drugs

• Effects of multiple ototoxic agents may be synergistic, antagonistic, and nonlinear

Platinum Ototoxicity

• Outer hair cells
• Several possible methods of entry into the hair cells

• With larger doses\cite{14}:
  • inner hair cells
  • supporting cells
  • stria vascularis
  • auditory nerve

Adapted from MC4324rev1115 and Dallos & Fakler, 2002
Symptoms of Platinum Ototoxicity

• Hearing Loss
  • Bilateral, irreversible, progressing from higher (> 8 kHz) to lower frequencies
  • Related to cumulative dose, though a single dose may cause hearing loss
  • May have a delayed onset

• Tinnitus
  • Transient or permanent (with or without hearing loss)

Audiological Evaluation

• Case History
• Otoscopic Examination
• Tympanometry (Acoustic reflexes and decay)
• Behavioral Audiometry (conventional, CPA, VRA)
  • Thresholds for pure tones (≤ 8 kHz)
  • Extended high frequency (up to 20 kHz)
• Speech Audiometry
• Otoacoustic Emissions (OAEs)
  • Byproduct of healthy outer hair cell function
• Auditory Brainstem Response (ABR) testing

Responsive
Full Assessment Subjective Measures Objective Measures
Behavioral Audiometry Otoacoustic Emissions (OAEs)

Limited
Limited Time Subjective Measures Objective Measures
Limited Behavioral Audiometry OAEs

Nonresponsive
Objective Measures Only
Auditory Brainstem Response (ABR) testing OAEs
Ototoxicity Monitoring

WHEN?

- Baseline evaluation
- Monitoring evaluations
- Post-treatment evaluations
- Long-term follow-up evaluations
Guidance

1994
Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy
Ad Hoc Committee on Audiologic Management of Individuals Receiving Otoxic and/or Vestibulotoxic Drug Therapy

2006
CHILDREN’S ONCOLOGY GROUP
American Academy of Audiology
Position Statement and Clinical Practice Guidelines
Otoxicity Monitoring

2009

ASHA (1994)
Significant Change Criteria

- Change in hearing thresholds relative to baseline
  - ≥ 20 dB decrease
  - ≥ 10 dB decrease
  - No response
  - ≥ 10 dB decrease
  - Three Frequencies

- Change confirmed by retest within 24 hours

Scales/Criteria/Grading

- Detection of change for an individual
- No agreed upon grading scale
  - Used to rank degree of ototoxicity
  - Report adverse events in clinical trials / hearing outcomes in groups
  - Provide government agencies with data for drug safety
  - Difficult to compare patients, disease groups, assess effectiveness of otoprotective drugs, etc.

ASHA (1994)
NCI CTCAE v4.03 (2010)
Children’s Cancer Group (1990)
AAA (2009)
SOP Boston Scale (2012)
Break Scale (1991)
Chang Scale (2010)
CHB (2009)

SIOP Boston Scale (2012)
Children’s Cancer Group (1990)
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ADULT GRADING
National Cancer Institute Common Terminology
Criteria for Adverse Events (CTCAE) v4.03

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>Threshold shift of 15-25 dB averaged at 2 contiguous test frequencies in at least one ear</td>
</tr>
<tr>
<td>2</td>
<td>Threshold shift &gt; 25 dB averaged at 2 contiguous test frequencies in at least one ear</td>
</tr>
<tr>
<td>3</td>
<td>Threshold shift &gt; 25 dB averaged at 3 contiguous test frequencies in at least one ear or therapeutic intervention indicated</td>
</tr>
</tbody>
</table>

* On a 1, 2, 3, 4, 6, and 8 kHz audiogram


PEDIATRIC GRADING
National Cancer Institute Common Terminology
Criteria for Adverse Events (CTCAE) v4.03

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<td>0</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>Threshold shift &gt; 20 dB at 8 kHz in at least one ear</td>
</tr>
<tr>
<td>2</td>
<td>Threshold shift &gt; 20 dB at 4 kHz or above in at least one ear</td>
</tr>
<tr>
<td>3</td>
<td>Threshold shift &gt; 20 dB at 3 kHz or above in at least one ear, or hearing loss requiring intervention including hearing aids and/or speech-language services</td>
</tr>
<tr>
<td>4</td>
<td>Hearing loss indication for a cochlear implant and/or additional speech-language services</td>
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</table>

* On a 1, 2, 3, 4, 6, and 8 kHz audiogram


PEDIATRIC GRADING
SIOP Boston Ototoxicity Scale

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

* Based on sensorineural hearing loss (SNHL) in dB HL; bone conduction or air conduction with normal tympanogram

Limited/Minimal Evaluations

- Influence of patient cooperation
- Maximizing essential auditory information
- Objective measures of hearing
- Shortened procedures\(^{6,15,20}\)
  - Emphasis on highest frequencies
  - Minimal test battery
  - Sensitive range for ototoxicity (SRO)
    - Highest frequency (≤100 dB SPL)
    - Next 6 lower adjacent frequencies in 1/6-octave increments (1 octave)

Factors/considerations

- Scheduling/coordination logistics
- Standard monitoring protocol
- Missing critical information
- Conductive component
- Test sequence/prioritization/methodology
- Influence of patient cooperation
- Access to clinical equipment/portability
- Determining a significant change/grading

Ototoxicity Monitoring

WHY?
Oncology Counseling

- Side effects of chemotherapy; including but not limited to:
  - Myelosuppression
  - Need for transfusion
  - Risk for transfusion
  - Nausea
  - Vomiting
  - Hair loss
  - Cardiac toxicity
  - Low risk of fertility issues
  - Renal failure
  - Seizures
  - Ototoxicity
  - And many more...

Children's Oncology Group
Family Handbook
https://childrensoncologygroup.org/index.php/cog-family-handbook

Counseling

- Potential impacts on the auditory system
  - Hearing loss
  - Realistic expectations
  - Other symptoms (tinnitus, fullness, dizziness)
- Signs and symptoms of cochlear damage and potential effects on communication ability
- Potentiating effects such as noise exposure during or following treatment
  - Hearing protection
- Informing caregivers (communication strategies)
Outcomes
• Type of testing (purpose)
• Behavioral and/or objective hearing change noted (confirmed by re-test)
• ASHA significant criteria
• Frequencies demonstrating ototoxic change
• Grading/Scaling
• Other symptoms (tinnitus, dizziness, etc.)

• Communicating to Health Care Team
  • Physician
  • Tumor Boards
  • Grand Rounds

Future?

Ototoxicity Monitoring
• WHO?
• WHAT?
• WHERE?
• WHEN?
• WHY?
There are several medications and chemicals known to be ototoxic.

Hearing loss is known to adversely impact quality of life, psychosocial functioning, and emotional well-being.

Summary

• Individual and societal costs of hearing loss are particularly grave in the case of children
  • Delayed speech, language, and educational development, need for special educational programs, continued medical care, etc.
  • Profound impact on the individual, his/her family, and society at large

Conclusions

• Ototoxicity monitoring permits:
  • Early identification of hearing loss
  • Classification of ototoxicity that can guide treatment decisions
  • Early intervention for hearing loss
  • Prevention of hearing loss

• Critical for the maintenance of quality of life and continued development
  • Leading to a reduction in the long-term impact of hearing loss


