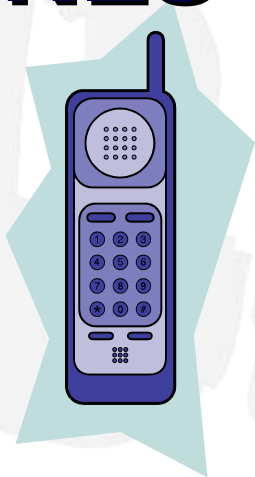
WELCOME!

PLEASE TURN OFF YOUR CELL PHONES & PAGERS



See page 7 of your Final Program for CEU Manager information.

Ototoxicity Monitoring

Using Behavioral & Objective Measures

VA Rehabilitation Research and Development

National Center for Rehabilitative Auditory Research

Course Presenters

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- Wendy J. Helt, M.A.
- Jane S. Gordon, M.S.
- Kelly M. Deal, M.S.
- Dawn Konrad-Martin, Ph.D.

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  - Brenda Lonsbury-Martin, Ph.D.

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Outline

I. Introduction (*Fausti*)

II. Principles of Ototoxicity Monitoring (*Fausti*)

III. Behavioral Ototoxicity Studies (*Helt*)

IV. Objective Monitoring (*Konrad-Martin*)

V. Monitoring Protocol (*Gordon*)

VI. Questions and Answers

National Center for Rehabilitative Auditory Research

Portland, Oregon VA Medical Center

One of 12 National RR&D Centers

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National Center for Rehabilitative Auditory Research

Mission

Alleviate the communicative, social and economic problems resulting from auditory system impairment

Principles of Ototoxicity Monitoring

Stephen A. Fausti, Ph.D.

Purpose for Ototoxicity Monitoring

For **<u>early detection</u>** of ototoxicity, to prevent the spread of hearing loss into frequencies important for speech communication

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Ototoxicity

- What is it?
- How much of a problem?
- Incidence of ototoxicity?
  - Methodological differences
  - Patient population
  - Criteria for change in hearing
  - Frequency range tested
  - Lack of uniformity of monitoring

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Types of Potentially Ototoxic Medications

- Chemotherapeutic agents
  - Cisplatin (CDDP)
  - Carboplatin
- Aminoglycoside antibiotics (AMG)
  - Gentamicin
  - Tobramycin
  - Amikacin
- Others

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How does ototoxicity present?

- Studies have shown high- to low- frequency progression of ototoxic hearing loss
- Studies have shown efficacy of high-frequency monitoring (Dreschler et al., 1989; Fausti et al. 1984; Jacobson et al., 1969; Ress et al., 1999; Tange et al., 1985; Van der Hulst et al., 1988; Fausti et al., 1993; Fausti et al., 1994)
- Studies have shown testing in 1/6-octave intervals provides earlier detection (Fausti et al., 2003; Vaughan et al., 2003)
- Our ototoxicity-monitoring protocol targets the upper frequency limit of hearing for testing in 1/6-octave steps

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Guidelines for the Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy

Committee on Ototoxicity and Vestibulotoxicity Management

American Speech-Language-Hearing Association

- Problem recognized by national organization
- Provides for standardized monitoring procedures

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Benefits of Ototoxicity Early Identification and Monitoring

- If change is observed, treatment modification can prevent further hearing loss
- If no change is observed, continued treatment warranted
- Early detection can prevent hearing damage which may interfere with communication
- Educates patients and health care providers
- Assists with preparing patient with realistic expectations
- Allows appropriate planning for rehabilitation

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Current Status of Ototoxicity Monitoring

- Few programs in existence
- Lack of uniform practices
- Primary care providers use serum levels to indicate ototoxicity

The only way to know if a person is losing their hearing is direct assessment of auditory function

Behavioral Ototoxicity Studies at the NCRAR

Portland VAMC

Wendy J. Helt, M.A., CCC-A

Current Status: A National Survey of VA Medical Centers

CONCERNS:

1) Uncertainty about an efficient, evidence-based protocol

2) Lack of audiologist staffing to provide time- and labor-intensive monitoring procedures

3) Lack of portable instrumentation
   - acutely ill patients prefer to remain in their hospital ward rooms or in their homes
   - increasingly, patients seen as outpatients or at home

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Research Goals

1) Develop methodology for *RELIABLE* and *SENSITIVE* early detection of ototoxicity
   - Behavioral component
   - Objective component

2) Identification of an abbreviated *TIME-EFFICIENT* test protocol

3) Development of a *PORTABLE* ototoxicity detection device

Response to Concern #1

Need for Efficient, Evidence-based Protocol

- RELIABILITY: TEST-RETEST
- SENSITIVITY

RELIABITY: TEST-RETEST (>8 kHz)

- Intra-subject threshold variability in sound-attenuating booth is generally:
  - Reported at around ± 5 dB for frequencies < 8 kHz
  - Increases slightly with increasing frequency > 8 kHz

Fausti SA, Henry JA, Hayden D, Phillips DS, Frey RH: Intrasubject reliability of high-frequency (9-14kHz) thresholds: tested separately vs. following conventional-frequency testing. *Journal of the American Academy of Audiology* 9:147-152, 1998.

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- Studies demonstrate > 96% of test-retest variability within ± 10 dB for frequencies between 9 to 14 kHz
  - Koss HV/1A earphones: (Fausti et al., 1998; Frank, 1990; Frank and Dreisbach, 1991; Gordon et al., under review)
  - Sennheiser HDA 200 earphones: (Frank, 2001)

- Threshold variations > ± 10 dB occurred most at 16 kHz and ranged from 1.1 to 4.6% (reviewed in Frank, 2001)

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SENSITIVITY

Purpose: To identify auditory frequencies at which serial threshold testing would provide the greatest sensitivity for early detection of ototoxicity

Fausti SA, Henry JA, Helt WJ, Phillips DS, Frey RH, Noffsinger D, Larson VD, Fowler CG: An individualized, sensitive frequency range for early detection of ototoxicity. *Ear & Hearing* 20:497-505, 1999.

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ASHA Criteria for Ototoxic Change

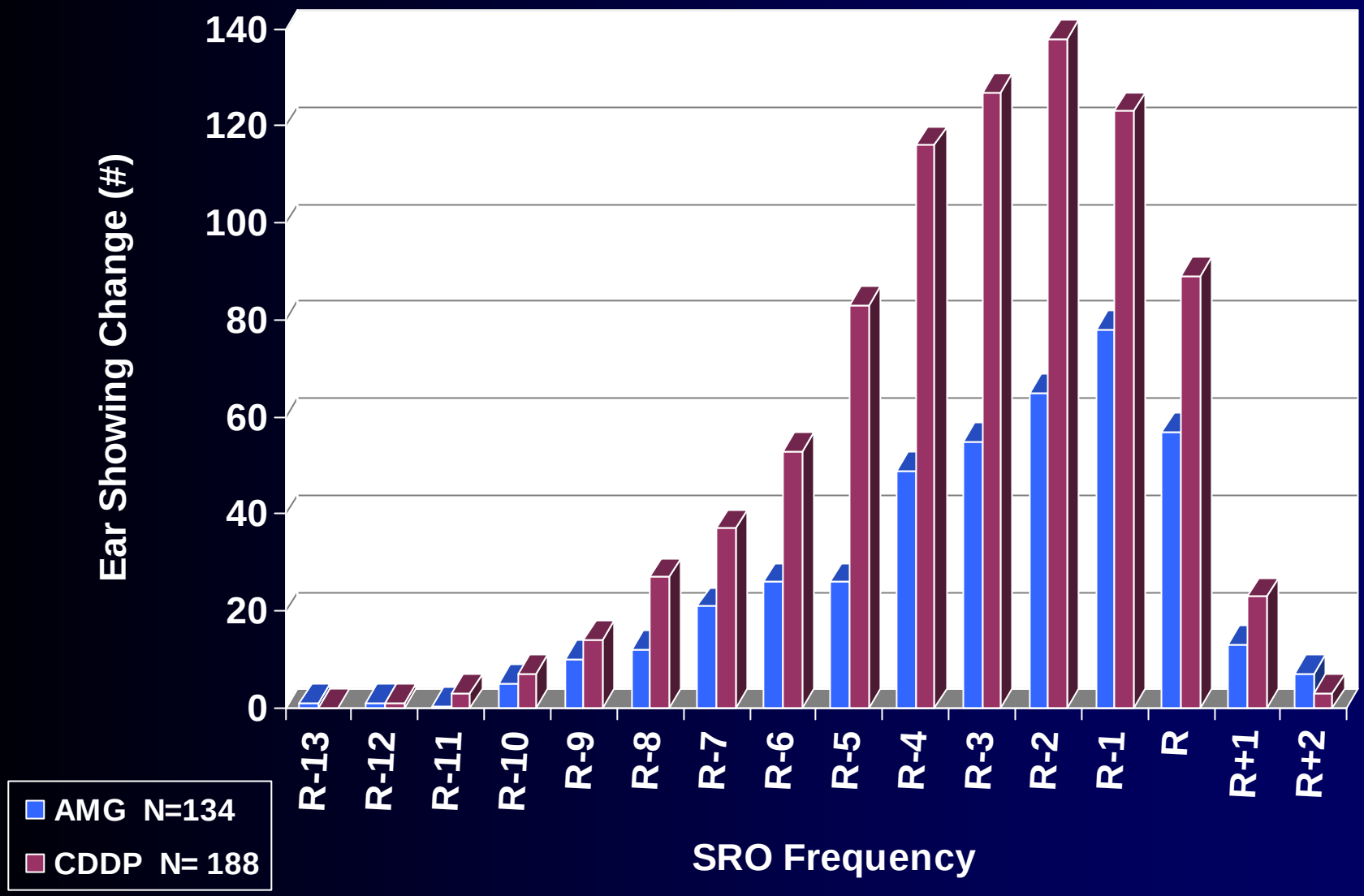
1) ≥ 20 dB change at 1 test frequency

2) ≥ 10 dB change at 2 adjacent test frequencies

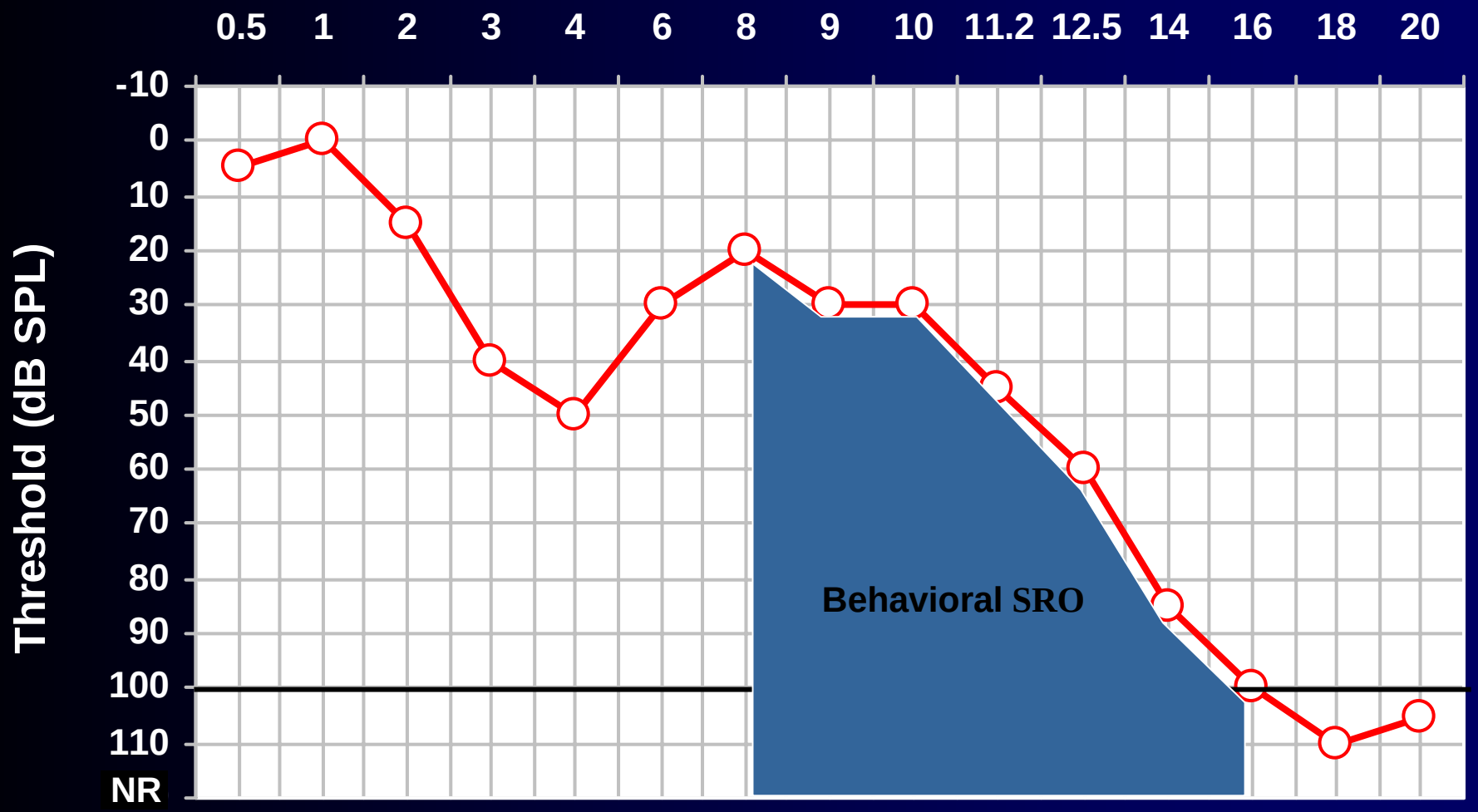
3) Loss of response at 3 consecutive test frequencies where responses were previously obtained

*Change confirmed by retest

Initial Ototoxicity Detection



Example SRO Above 8 kHz



Results

- Thresholds > 100 dB SPL generally stable
- Most initial changes seen in a limited frequency range ≤ 100 dB SPL
- Range for each individual is unique and specific to their hearing configuration
- A sensitive range for ototoxicity (SRO) is the uppermost frequency with a threshold ≤100 dB SPL and 6 lower consecutive frequencies
- ~ 90% *initial* ototoxicity detection occurs within the SRO

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Purpose: To determine if adding 1/6-octave testing below 8 kHz would increase the ototoxicity detection rate for patients with poorer hearing

Fausti SA, Helt WJ, Phillips DS, Gordon JS, Bratt GW, Sugiura KM, Noffsinger D: Early Detection of Ototoxicity Using 1/6-Octave Steps. *Journal of the American Academy of Audiology* 14:444-450, 2003.

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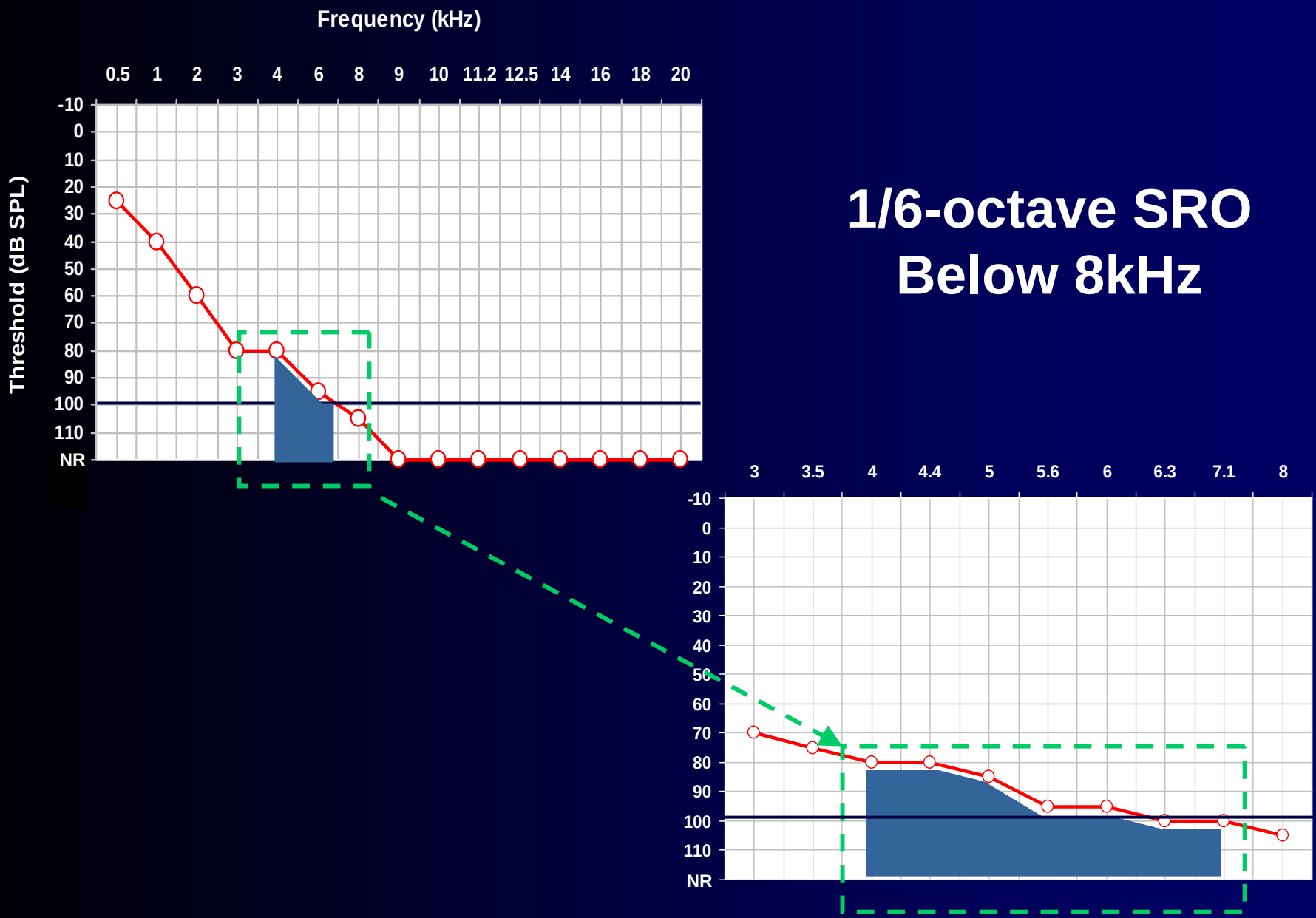
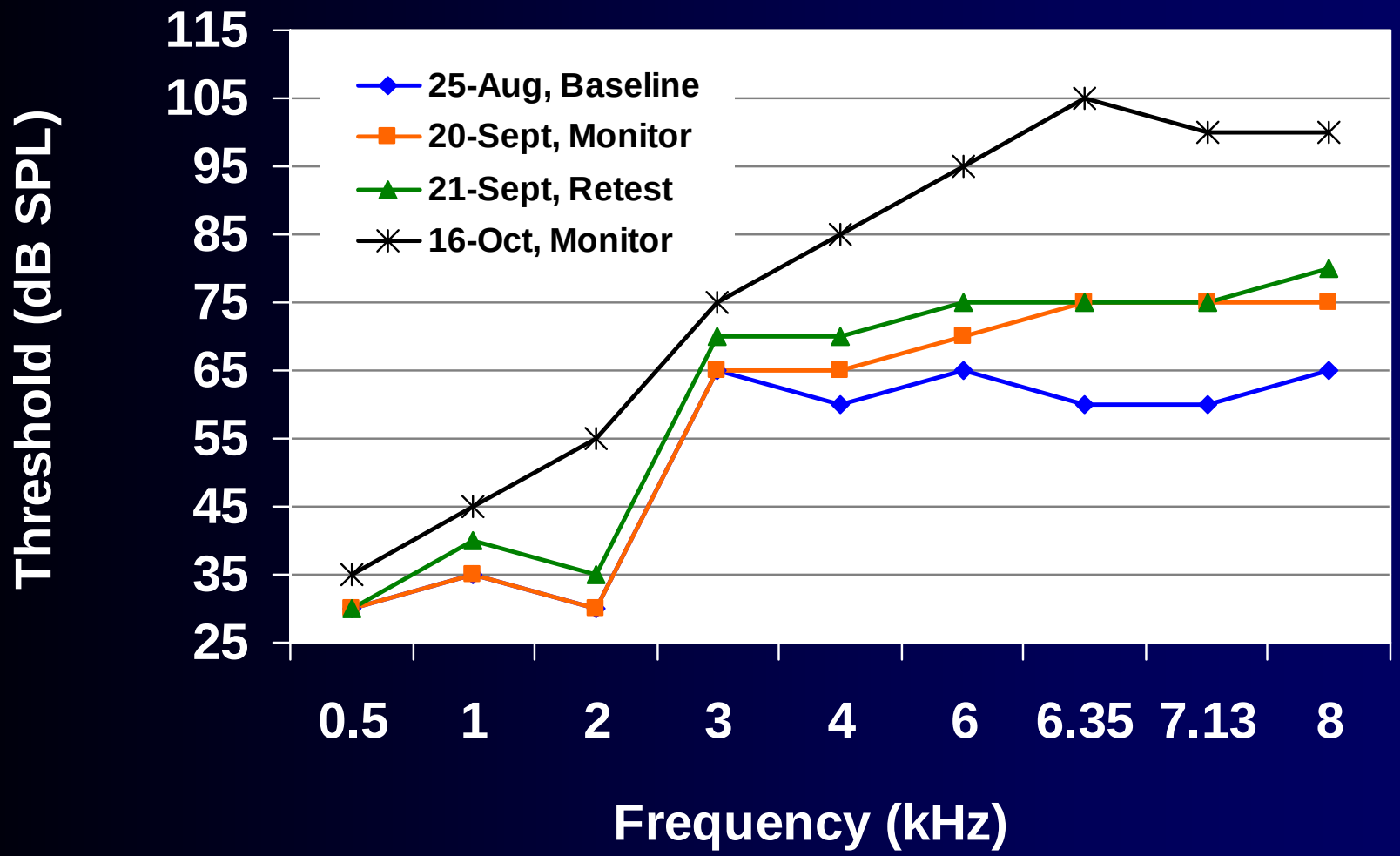


1/6-octave SRO Below 8kHz

Case Example of Ototoxic Threshold Shifts: SRO Below 8 kHz



Case Example: Comparison of Conventional and 1/6-Octave Protocol

	Change From Baseline (dB SPL)	
Test Frequency (kHz)	**Conventional Frequency Protocol**	**1/6-Octave Protocol**
0.50	0	0
1.00	0	0
2.00	0	0
3.00	0	0
4.00	+5	+5
6.00	+5	+5
6.35	Not applicable	**+15**
7.13	Not applicable	**+15**
8.00	+10	**+10**

Results

Conventional Frequency Testing Only

- **Initial ototoxic hearing change missed or detected later in 76/210 ears**

	AMG (N=25 ears)	Cisplatin or Carboplatin (N=185 ears)
Percentage of Ears Missed or Detected Later	28%	37%

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Initial Ototoxicity Detection Using SRO

(Above and Below 8kHz)

	Total (Ears)	Hit	Miss	Initial Change on SRO
AMG	54	46	8	85%
Cisplatin	226	207	19	92%
Carboplatin	59	50	9	85%
Total	339	303	36	89%

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False Positive Rate for ASHA Criteria: *Sound Booth*

	≥ 20 dB at 1 Frequency	≥ 10 dB at 2 consecutive frequencies	Frequency Range
Koss PRO/4X*	0%	0%	2, 5-16 kHz
ER-4B*	0%	0%	2, 5-16 kHz
Sennheiser HAD 200**	0%	2%	8-16 kHz

*Gordon JS, Phillips DS, Helt WJ, Fausti SA: The evaluation of insert earphones for high-frequency bedside ototoxicity monitoring. *JRR&D*, under review.

**Frank T: High-Frequency (8 to 16 kHz) reference thresholds and intrasubject threshold variability relative to ototoxicity criteria using Sennheiser HAD 200 earphone. *Ear & Hearing* 22 (2): 161-168, 2001.

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Response to Concern #2

Need for Time-Efficient Protocol

- 90% detection rate for initial ototoxic change
- Fast relative to conventional full frequency testing

Conventional: 0.5 - 20kHz;
15 Frequencies

SRO: 1 octave in 1/6th octave steps;
7 frequencies

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Response to Concern #3

Portability of Instrumentation

Purpose: 1) To develop a portable, handheld audiometer-like device that will enable time-efficient, reliable and sensitive early detection of ototoxicity.

Purpose: 2) To evaluate the use of insert earphones for obtaining reliable threshold responses at bedside in the hospital room.*

***Gordon JS, Phillips DS, Helt WJ, Fausti SA: The evaluation of insert earphones for high- frequency bedside ototoxicity monitoring. *JRR&D*, under review.**

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Ototoxicity Identification Device (Oto-ID)

False Positive Rate for ASHA Criteria: *Ward*

	≥ 20 dB at 1 Frequency	≥ 10 dB at 2 Consecutive Frequencies	Frequency Range
Koss PRO/4X*	0%	7%	2, 5-16 kHz
ER-4B*	0%	0%	2, 5-16 kHz

***Gordon JS, Phillips DS, Helt WJ, Fausti SA: The evaluation of insert earphones for high-frequency bedside ototoxicity monitoring. *JRR&D*, under review.**

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Conclusions
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1) Evidence-based protocol

2) Time-efficient protocol

3) Portability

- High frequencies are reliable
- Sensitive Range for Ototoxicity (SRO) exists
- ~90% initial detection rate using SRO
- Only 7 frequencies in SRO
- Earphones can be used on ward
- OtoID

Objective Measures for Ototoxicity Monitoring

Portland VAMC

Dawn Konrad-Martin, Ph.D., CCC-A

Objective Monitoring DPOAE

- Potential advantages
  - Rapid
  - Frequency specific
  - Tests cochlear biomechanical response to sound
  - Earliest detection (?)

Objective Monitoring DPOAE

- Potential disadvantages
  - High-frequency measurements difficult
  - Limited to assessment of OHC system function
  - DPOAE amplitudes linked to hearing sensitivity only for thresholds < about 60 dB HL
  - Hearing loss may preclude measurable responses

DPOAE Sensitivity

- Link between ototoxic DPOAE changes and OHC changes (for review see Whitehead et al., 1996)
- Conventional audiometric changes occurred later relative to OAE, or not at all (AMG: Katbamna et al., 1999; Stravroulaki et al., 2002; Mulheran & Degg, 1997; CDDP: Ress et al., 1999)
- Compared to behavioral testing within the high frequency (> 8000 Hz) range, DPOAEs showed effects of ototoxicity in a similar proportion of ears (Ress et al., 1999)

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Are DPOAE a Sensitive Indicator of Ototoxic Hearing Change?

- *Aim 1*: For adult patients with demonstrated ototoxic hearing change, determine whether DPOAE change occurred (e.g., hit rate)
- *Aim 2*: Determine the relationship between baseline puretone threshold and DPOAE in the DP “Hit Group” and the DP “Miss Group”
- *Aim 3*: Determine whether an individualized sensitive region for ototoxicity (SRO) exists for DPOAE measurement

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Methods

- Subjects:
  - 53 subjects (90 ears) with demonstrated ototoxic hearing change
- Behavioral testing:
  - Puretone thresholds at .5-20 kHz
  - SRO: Top frequency with a threshold of $\leq$ 100 dB SPL, 6 lower 1/6-octave frequencies
  - Criteria for change: ASHA 1994 Guidelines
- DPOAE testing:
  - f2 varied 0.8-8 kHz; f2/f1=1.22; L1, L2=65, 59
  - Response: Amplitude $\geq$ -10dB SPL; SNR > 6 dB
  - Criteria for Change: 4 dB change in amplitude or loss of response relative to baseline at *two* consecutive frequencies

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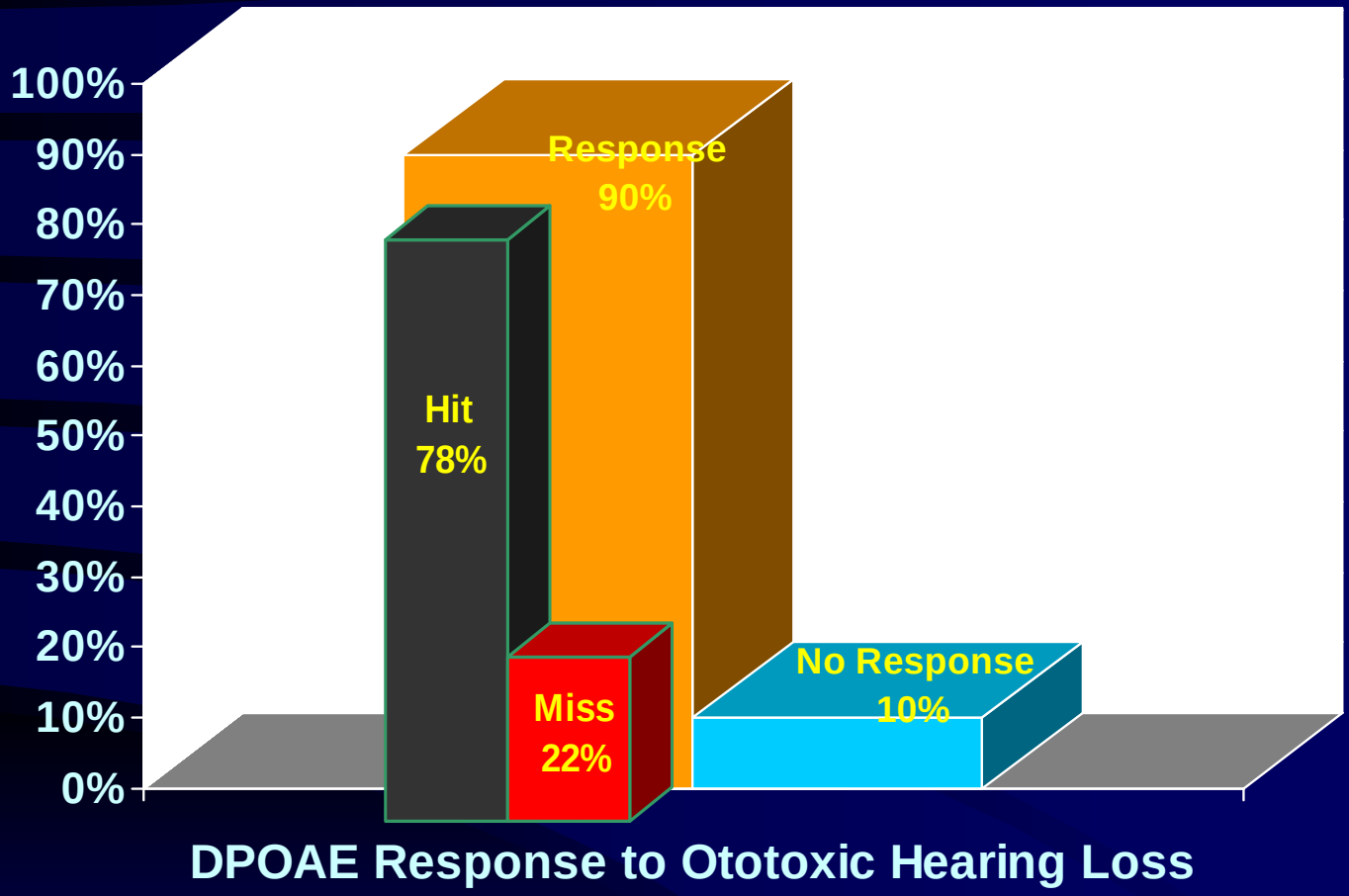
Results: *DPOAE Sensitive?*



Hit: N = 63 Miss: N = 18 No Response: N = 9

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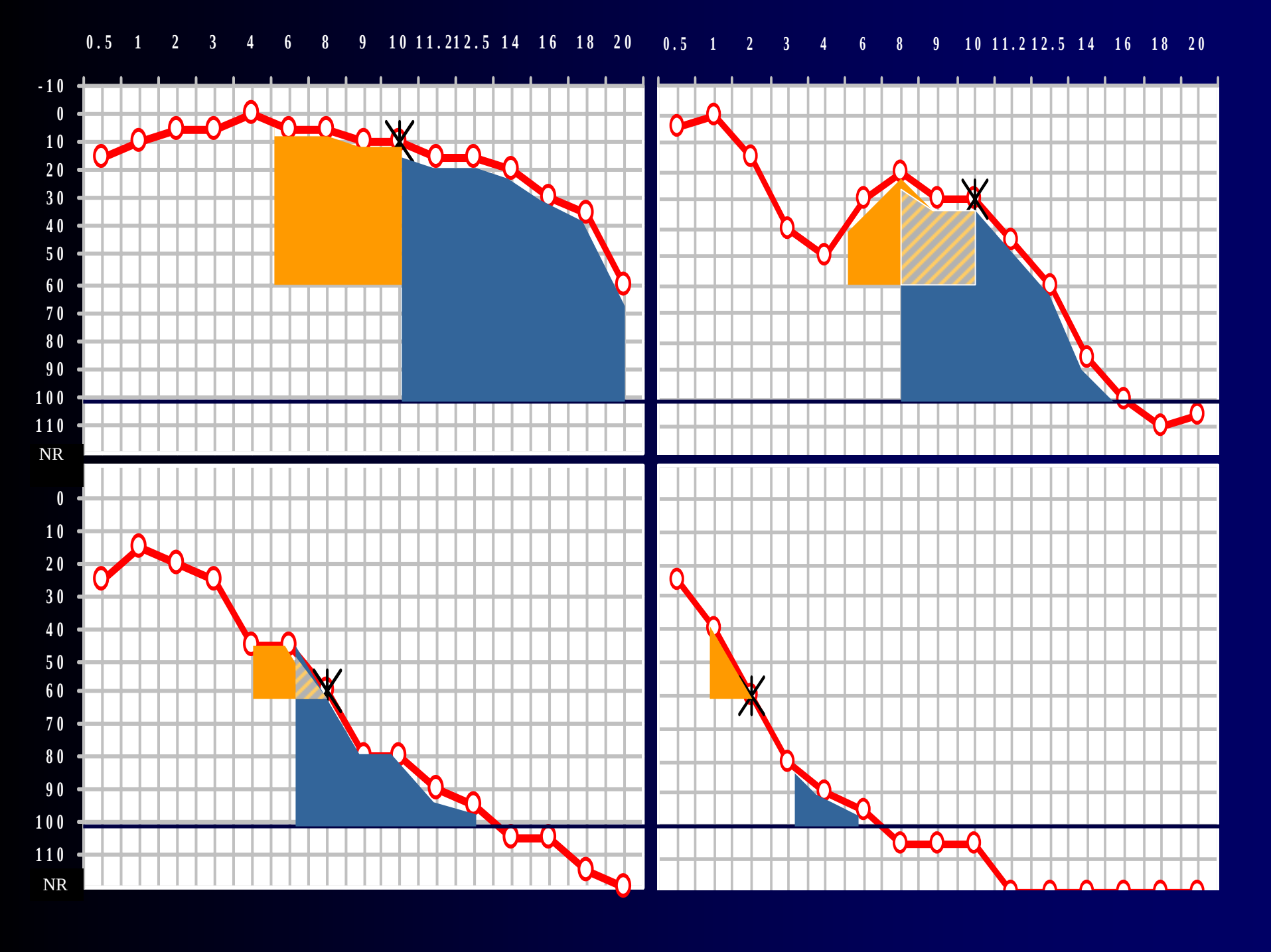
0.5 1 2 3 4 6 8 9 10 11.2 12.5 14 16 18 20
0.5 1 2 3 4 6 8 9 10 11.2 12.5 14 16 18 20
-10
0
10
20
30
40
50
60
70
80
90
100
110
NR
0
10
20
30
40
50
60
70
80
90
100
110
NR

Results: *DPOAE Relationship to Puretone Thresholds?*

DPOAE Hit group characterized by:

- Top DP frequency closer to behavioral SRO (*p < 0.05)*
- Higher Top DPOAE Frequency ($p < 0.01$)
- More Valid DPOAE Responses (*p < 0.01)*
- Better Behavioral Thresholds (*p < 0.01)*
- Larger threshold differences between top and bottom b-SRO (*p < 0.01)*, related to the slope of the thresholds near the upper frequency limit of hearing

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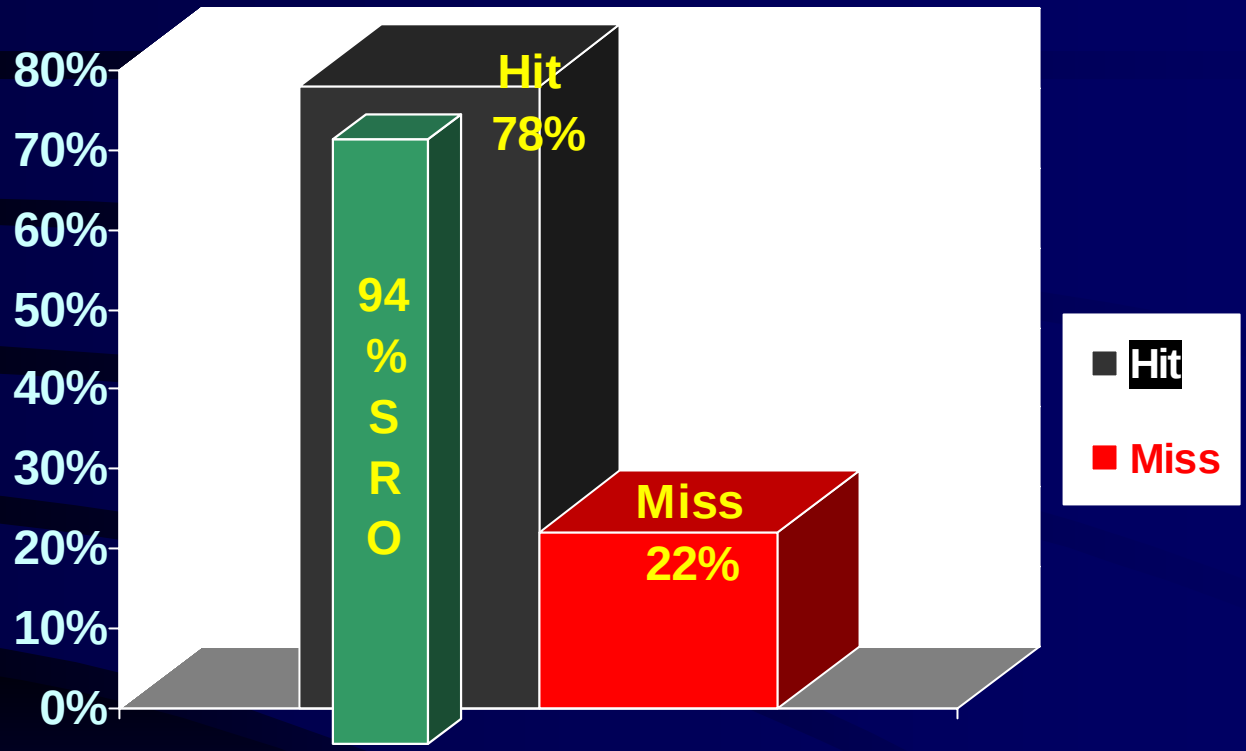
Results: *DPOAE SRO?*



94% of the DPOAE that reflect change, did so within an octave of the highest DP frequency able to elicit a response.

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DPOAE Measurement

- DPOAE reliability depends to a large degree on understanding effects of
  1. Subject noise
  2. System distortion
  3. Probe fit

- Need to get familiar with the way DPOAEs are physically measured
  - Kemp et al., Seminars in Hearing, 1992
  - Don’t forget your friendly system rep

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DPOAE Measurement

- Noise floor
  - Usually the average amplitude in several frequency bins above and below the 2f1-f2 bin
- Signal-to-noise ratio (SNR)
  - dB difference between SPL at 2f1-f2 and the estimated noise
  - To be valid, a DPOAE should have a favorable SNR (e.g., 6 dB, or even 10 dB)
- System distortion levels
  - To be valid, a DPOAE should be higher than this
- Response requires averaging
  - Average until noise floor is at about the level of your system distortion (e.g., -20 dB SPL) or artifact-free averaging time reaches 32 seconds

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DPOAE Validation

- Criteria for a valid response
  1. Favorable SNR (e.g., 6 dB, or 10 dB in noisy environment)
  2. Conservative estimate of YOUR system distortion (e.g., for our system is –20 dB SPL)
- DPOAE must meet these criteria to be considered a valid test of cochlear function
- Repeat system distortion measurements frequently to assess system performance

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DPOAE Reliability

- How much DPOAE variation is due to random variability, variability due to probe placement?
- Depends in part on probe fit
  - Firm vs loose
  - Ports facing TM vs ports blocked
  - Middle ear function (can fluctuate)
  - Subject noise and SNR (averaging time)
  - Frequency

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DPOAE Reliability

To determine how much DPOAE variation is due to random variability and probe placement

- Standard error of measurement (SEM)
  - Typically about 2-3 dB for frequencies between 1 and 4 kHz (Franklin et al. 1992; Beattie et al., 2003)
- Construct confidence intervals
  - e.g. ~68% chance change > 1 SEM, ~95% chance chance change > 2 X SEM not due to random variability

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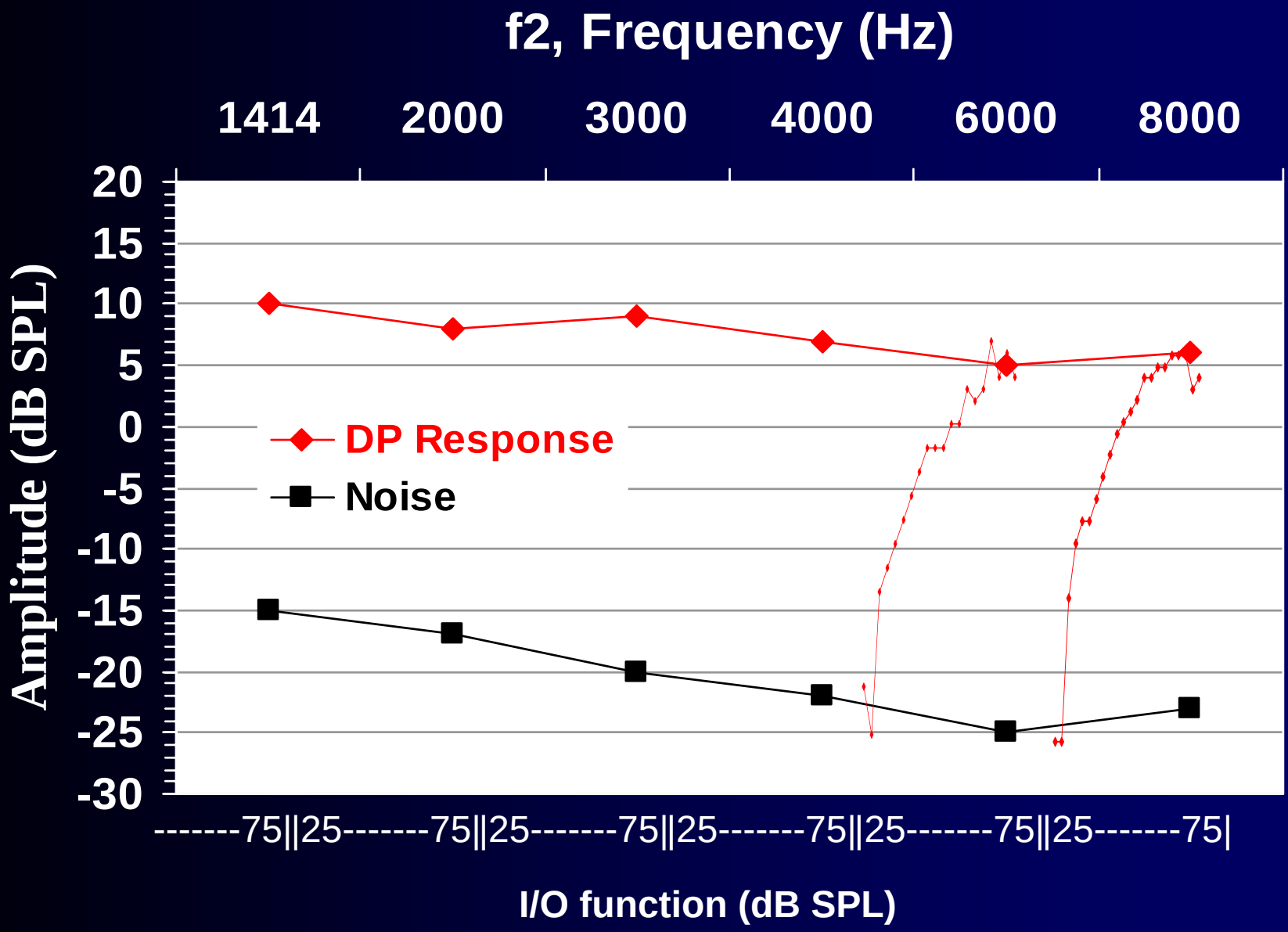
f2, Frequency (Hz)
1414
2000
3000
4000
6000
8000
20
15
10
5
0
-5
-10
-15
-20
-25
-30
Amplitude (dB SPL)
DP Response
Noise
-------75||25-------75||25-------75||25-------75||25-------75||25-------75|
I/O function (dB SPL)

Response to Survey Concerns

Need for Efficient, Evidence-based Protocol

- PROTOCOL
  - Still need (1) standards for DPOAE and ABR testing and (2) Objective Criteria for ototoxic change
  - DP-gram at moderate level (e.g., L1, L2 in dB SPL = 60,60), f2 varied in ½-octave steps
  - Define DP-SRO, 1/6th-octave within SRO
  - I/O functions within SRO may improve sensitivity, but we don't know yet

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Response to Survey Concerns

Need for Efficient, Evidence-based Protocol

- TIME EFFICIENCY
  - Yes
- SENSITIVITY
  - Estimate in large groups of subjects receiving ototoxic drugs
- RELIABILITY: TEST-RETEST
  - Estimate test-retest and false positive rates in large group of hospitalized controls

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Break

Ototoxicity Early Detection and Monitoring

Jane S. Gordon, M.S., CCC-A

Important Considerations

- Patient Status
  - Responsive
  - Limited responsive
  - Unresponsive
- Characteristics of Tests
  - Reliable
  - Sensitive
  - Clinically time-efficient

Basic Requirements

- Determine patient status
- Test location and equipment
- Patient identification/contact
- Patient testing
- Behavioral hearing change criteria and objective measure change criteria
- Patient counseling
- Report to primary care provider (PCP)
- Patient tracking

Patient Status Determines Test Protocol

- Responsive: Full audiometric evaluation, including extended high frequencies >8 kHz (EHF), and SRO
- Limited Responsive: As much of auditory evaluation as possible (otoscopy, tympanometry, acoustic reflexes, EHF and SRO, and DPOAE or ABR)
- Non-responsive: Objective measures only (otoscopy, tympanometry, acoustic reflexes, DPOAE or ABR)

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Test Location and Equipment

- Soundbooth versus ward
- Maintain consistent conditions / document
- Audiometer / high-frequency headphones
- Immittance system
- OAE system or ABR system
- Calibration

Patient Identification

- Coordinated effort between the audiologist and health care team
- Medical staff
  - Oncologist / PCP
  - Nurse
  - Pharmacist
- Computer generated pharmacy lists

Patient Contact

- Introductions and Information
  - Purpose
  - Benefits
  - Procedures
- Coordination
  - Work with nurse
  - Identify scheduling conflicts

Patient Testing

- Baseline evaluation
  - 24 hour recheck evaluation
- Monitor evaluations
  - Performed periodically throughout treatment
- Post-treatment evaluations
  - Immediate post-drug evaluation
  - 1 month follow-up evaluation
  - 3 month follow-up evaluation
  - 6 month follow-up evaluation

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Baseline Evaluation

- Time obtained
  - AMG patients within 72 hours
  - CDDP and Carboplatin patients within 24 hours
- Tests obtained
  - Case history
  - Tinnitus and Noise Questionnaire
  - Otoscopy
  - Tympanometry and Acoustic Reflex
  - Puretone AC (>8 kHz); identify 1/6-octave SRO
  - Puretone BC
  - Speech reception thresholds
  - Word recognition
  - DPOAE or ABR
- 24 hour Baseline Re-check

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Monitor Evaluations

- Time obtained
  - Performed periodically
  - AMG: every 2-3 days, minimum once a week
  - CDDP/Carboplatin: Each dose
- Tests obtained
  - Tinnitus and noise questionnaires
  - Otoscopy
  - Tympanometry and Acoustic Reflexes
  - Puretone AC and SRO

If changes in hearing are noted

  - Puretone BC
  - Speech testing

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Post-treatment Evaluations

- Time obtained
  - Immediately at discontinuation of drug treatment
  - One month follow-up
  - Three month follow-up
  - Six month follow-up
- Re-test if ASHA-significant changes noted
  - Continue to monitor until hearing stabilized
- Tests obtained
  - Include the same tests as “monitor evaluations”

Change Criteria

- ASHA Ototoxic Change Criteria
  - ≥20 dB shift at one frequency
  - ≥10 dB shift at 2 consecutive test frequencies
  - “Response” shifting to “no response” at 3 consecutive test frequencies
  - Change confirmed by retest
- DPOAE and ABR Ototoxic Change Criteria
  - Determine YOUR own test-retest criteria
  - SEM x 2 for 95% confidence

Each subject will serve as their own control

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Patient Counseling

- Hearing loss
  - Potential recovery
  - Permanent
  - Realistic expectations
- Other symptoms (tinnitus, dizziness)
- Noise potentiation
  - Use ear protection
  - Up to 6 months
- Amplification
  - Caution against over-amplification

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Report to Primary Care Provider

- Test results
  - Type of test
- Behavioral hearing change noted
  - ASHA significant criteria
  - Frequencies demonstrating ototoxic change
  - Confirmed by re-test
- Objective hearing change noted
  - Exceeds your established test-retest reliability
- Other symptoms
  - Dizziness
  - Tinnitus

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Patient Tracking

- Medical staff participation
- Computer generated
- Hardcopy scheduling
- Patient contact; schedule at end of current appointment

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Patient Issues

- Patient transport
- Fragility of patients
- Patient time constraints
- Shortened testing
  - Limited frequency
  - Target frequency

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Conclusion

- Need for monitoring programs
- Procedures exist
- Audiologists must:
  - Promote
  - Establish
  - Manage

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Questions and Answers

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